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This report evaluates scientific information on direct health effects associated with exposure to acid aerosols. Although the literature up to 1987 has been reviewed thoroughly for information relevant to acid aerosols, the present report is not intended as a complete and detailed review of all literature pertaining to acid aerosols. Rather, an attempt has been made to focus on the evaluation of those studies providing key information on health effects and aerometrics. This report includes discussion of: the physical and chemical properties of acid aerosols; ambient monitoring techniques and ambient concentrations; the toxicology of acid aerosols in experimental animals, including a discussion of information on deposition and neutralization of acid aerosols; assessment of epidemiological studies of health effects of acid aerosols; assesment of controlled human exposure studies evaluating the effects of acid aerosols; and a summarization of the above information with appropriate interpretations and conclusions. Lastly, important research needs are identified which are critical to be addressed in order to improve the data base for acid aerosols and associated health effects as a basis for decisions on whether to list acid aerosols as a criteria pollutant for development of criteria and national ambient air quality standards.

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CONTENTS

Page

TABLES vii
FIGURES x
ABSTRACT xii
AUTHORS, CONTRIBUTORS, AND REVIEWERS xiii

1. INTRODUCTION 1-1

2. STRONG ACID AEROSOLS: CHARACTERIZATION AND EXPOSURE 2-1
  2.1 INTRODUCTION 2-1
  2.2 CHEMICAL AND PHYSICAL PROPERTIES OF ACID AEROSOLS 2-2
    2.2.1 Formation of Acid Sulfates 2-2
    2.2.2 Particle Size of SO_4^{2-} and H^+ 2-7
    2.2.3 Formation of Nitric Acid 2-12
    2.2.4 Acid Fogs 2-12
    2.2.5 Neutralization 2-17
  2.3 METEOROLOGY 2-23
  2.4 EMISSION DENSITIES AND DISTRIBUTION 2-25
    2.4.1 Sulfur and Nitrogen Oxide Emission Densities 2-25
    2.4.2 Sulfate Distribution 2-25
  2.5 HISTORIC ACID LEVELS 2-29
    2.5.1 London Sulfuric Acid Data 2-29
    2.5.2 Los Angeles Data 2-33
  2.6 METHODOLOGY FOR STRONG ACID MEASUREMENT 2-33
    2.6.1 Methodologies for Strong Acids and Sulfuric Acids 2-34
      2.6.1.1 Sulfuric Acid 2-34
        2.6.1.1.1 Filter collection 2-34
        2.6.1.1.2 Extraction with pH measurement or H^+ titration 2-35
        2.6.1.1.3 Specific extraction of atmospheric acids 2-35
        2.6.1.1.4 Specific extraction with derivatization 2-36
        2.6.1.1.5 Continuous and/or real-time analysis 2-36
      2.6.1.2 Nitric Acid 2-37
        2.6.1.2.1 Nitric acid sampling techniques 2-37
    2.6.2 Sampling Anomalies 2-39
      2.6.2.1 Sorption Losses 2-39
      2.6.2.2 Equilibria-Driven Losses 2-40
    2.6.3 Recommended Protocols 2-40
      2.6.3.1 Strong Acid Aerosols 2-40
      2.6.3.2 Specific Determination of H_2SO_4 2-41
    2.6.4 Applications 2-41

CONTENTS (continued)

Page

2.7 ATMOSPHERIC CONCENTRATION 2-42
  2.7.1 Atmospheric Acidic Sulfate Studies from 1974 to 1986 2-42
  2.7.2 Acid Sulfate Exposure and Events 2-51
  2.7.3 Atmospheric Nitric Acid Concentration 2-57
2.8 SUMMARY 2-58
  2.8.1 Implications for Atmospheric Pollution Studies 2-62
2.9 REFERENCES 2-63

3. DEPOSITION AND FATE OF INHALED ACID AEROSOLS IN THE RESPIRATORY TRACT 3-1
3.1 INTRODUCTION 3-1
3.2 PARTICLE DEPOSITION MECHANISMS AND PATTERNS 3-2
3.3 HYGROSCOPIC AEROSOLS 3-9
3.4 NEUTRALIZATION BY AIRWAY SECRETIONS AND ABSORBED AMMONIA 3-10
  3.4.1 Airway Surface Liquid Buffering 3-11
  3.4.2 Ammonia Neutralization of Inhaled Acid 3-14
3.5 CONCLUSIONS 3-19
3.6 REFERENCES 3-20

4. TOXICOLOGICAL STUDIES OF ACID AEROSOLS 4-1
4.1 INTRODUCTION 4-1
4.2 MORTALITY 4-3
4.3 PULMONARY FUNCTION 4-5
4.4 RESPIRATORY TRACT MORPHOLOGY AND BIOCHEMISTRY 4-14
4.5 RESPIRATORY TRACT DEFENSES 4-21
  4.5.1 Clearance Function 4-22
    4.5.1.1 Conducting Airways - Mucociliary Clearance 4-23
    4.5.1.2 Respiratory Region 4-30
  4.5.2 Immunologic Defense 4-34
4.6 EFFECTS OF MIXTURES CONTAINING ACID AEROSOLS 4-35
4.8 SUMMARY AND CONCLUSIONS 4-43
4.9 REFERENCES 4-47

5. CONTROLLED HUMAN EXPOSURE STUDIES OF ACID AEROSOLS 5-1
5.1 INTRODUCTION 5-1
5.2 PULMONARY FUNCTION EFFECTS OF H_2SO_4 IN NORMAL SUBJECTS 5-3
5.3 EFFECTS OF ACID AEROSOLS ON BLOOD BIOCHEMISTRY 5-6
5.4 EXPOSURE TO MIXTURES OF ACID AEROSOLS WITH OTHER POLLUTANT GASES 5-13
5.5 EXPOSURE TO OTHER ACID AEROSOLS OR MIXTURES OF AEROSOLS 5-15
  5.5.1 Nitrates 5-15
  5.5.2 Other Sulfates 5-16
5.6 EFFECTS OF ACID AEROSOLS ON RESPIRATORY FUNCTION OF ASTHMATICS 5-18
5.7 EFFECT OF ACID AEROSOL INHALATION ON PULMONARY CLEARANCE MECHANISMS 5-29

CONTENTS (continued)

Page

5.8 EFFECTS OF SULFURIC ACID AEROSOL ON AIRWAY REACTIVITY 5-38
5.9 SUMMARY AND CONCLUSIONS 5-40
5.10 REFERENCES 5-42

6. EPIDEMIOLOGY STUDIES OF HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO ACID AEROSOLS 6-1
  6.1 INTRODUCTION 6-1
  6.2 ACUTE EFFECTS STUDIES 6-2
    6.2.1 Acute Episode Studies 6-2
      6.2.1.1 Meuse Valley 6-2
      6.2.1.2 Donora 6-2
      6.2.1.3 London Acid Aerosol Fogs 6-3
    6.2.2 European Acid Event of 1985 6-6
    6.2.3 Acute Exposure Studies of Children 6-7
    6.2.4 Acute Studies Relating Health Effects to Sulfates .. 6-11
  6.3 CHRONIC EXPOSURE EFFECTS STUDIES 6-13
    6.3.1 Acid Mists Exposure in Japan 6-13
    6.3.2 Chronic Studies Relating Health Effects to Sulfates 6-14
    6.3.3 Chronic Studies Relating Health Effects to Oxides of Nitrogen 6-21
    6.3.4 Chronic Exposure Effects in Occupational Studies ... 6-23
  6.4 SUMMARY AND CONCLUSIONS 6-24
  6.5 REFERENCES 6-29

7. CONSIDERATIONS FOR LISTING ACID AEROSOLS AS A CRITERIA POLLUTANT 7-1
  7.1 INTRODUCTION 7-1
    7.1.1 Purpose 7-1
    7.1.2 Background 7-1
    7.1.3 Approach 7-2
  7.2 CONSIDERATIONS FOR LISTING ACID AEROSOLS UNDER SECTION 108 OF THE CLEAN AIR ACT 7-2
    7.2.1 Characterization of Acid Aerosols 7-2
    7.2.2 Available Health Effects Data on Acid Aerosols 7-7
      7.2.2.1 Respiratory Mechanics and Symptoms 7-9
      7.2.2.2 Host Defense Mechanisms 7-13
      7.2.2.3 Morphological and Biochemical Alterations 7-15
      7.2.2.4 Aggravation of Existing Disease or Illness 7-18
      7.2.2.5 Mortality 7-20
      7.2.2.6 Summary of Health Effects 7-23
    7.2.3 Sources of Acid Aerosols 7-25
    7.2.4 Implications of Listing Acid Aerosols 7-26
  7.3 ALTERNATIVE APPROACHES FOR A LISTING DECISION 7-26
  7.4 REFERENCES 7-29

CONTENTS (continued)

Page

8. RESEARCH NEEDS 8-1
    8.1 CHARACTERIZATION AND EXPOSURE 8-1
    8.2 ANIMAL TOXICOLOGICAL STUDIES 8-5
    8.3 CONTROLLED HUMAN EXPOSURE STUDIES 8-8
    8.4 EPIDEMIOLOGY STUDIES 8-10

TABLES

Number **Page**

2-1 Important reaction rates for oxidation of sulfur dioxide 2-3

2-2 Aqueous SO_2 oxidation rates in the atmosphere 2-4

2-3 Classification of major chemical species associated with atmospheric particles 2-8

2-4 Summary of fogwater composition measurements 2-15

2-5 Estimated H_2SO_4 $(NH_4)HSO_4$ and $(NH_4)_2SO_4$ concentrations based on TA-FPD and quartz filter measurements at Sterling Forest 2-22

2-6 Description of sampling systems and instruments that measure chemical species that contribute to acidic dry deposition ... 2-38

2-7 A summary of representative North American atmospheric studies during which acid sulfate or total acidity was measured by one or more techniques 2-43

2-8 Concentration ranges of SO_4^{2-}, H^+ (as H_2SO_4) and H_2SO_4 (in $\mu g/m^3$) measured in various locations in North American 2-45

2-9 Acid events ($H_2SO_4 \geq 1\ \mu g/m^3$ for ≤ 2 h) 2-50

2-10 Episodic acidic aerosol data and estimates of exposure from selected acid sulfate classified by sampling time. Only periods where concentrations exceeded 5 $\mu g/m^3$ of apparent H_2SO_4 are used as events 24 hour data 2-53

2-11 Twelve hour acid aerosol data and estimates of exposure 2-54

2-12 Six hour acid aerosol date and estimates of exposure 2-54

2-13 Four hour acid aerosol data and estimates of exposure 2-55

2-14 One hour acid aerosol data and estimates of exposure 2-55

2-15 Four-, eight- and sixteen-hour acid aerosol data and estimates of exposure 2-56

2-16 Results of Columbus ambient air sampling 2-59

3-1 Model estimates of neutralization of 0.5 and 5.0 μm particles by "oral" and "nasal" levels of ammonia (Adapted from Cocks and McElroy, 1984) 3-18

TABLES (continued)

Number Page

4-1 Effect of H_2SO_4 particle size on mortality 4-3

4-2 Effects of acid aerosols on pulmonary function 4-6

4-3 Effects of acid aerosols on respiratory tract morphology 4-15

4-4 Effects of acid aerosols on tracheal clearance 4-24

4-5 Effects of acid aerosols on bronchial clearance 4-25

4-6 Effects of acid aerosols on bacterial infectivity in mice ... 4-31

4-7 Toxicologic interactions to mixtures containing acid aerosols 4-36

5-1 Summary of controlled human exposure studies of acid aerosols 5-7

5-2 Summary of characteristics of asthmatic subjects participating in acid aerosol studies (1979-1987) 5-20

5-3 Analysis of covariance of ten adolescent asthmatics exposed via mouth piece to 110 $\mu g/m^3$ sulfuric acid aerosol 5-23

5-4 A summary of the percentage change in pulmonary functional values after 10 minutes of moderate exercise 5-25

6-1 Acute health effects seen under conditions of measured or presumed acid aerosol exposure 6-25

6-2 Chronic health effects seen under conditions of measured or presumed acid aerosol exposure 6-26

7-1 Possible indicators to measure acid aerosols and characterize exposure 7-4

7-2 Effects of acid aerosols (<1,000 $\mu g/m^3$) on respiratory mechanics and symptoms 7-11

7-3 Effects of acid aerosols (<1,000 $\mu g/m^3$) on host defense mechanisms 7-14

7-4 Effects of acid aerosols (<1,000 $\mu g/m^3$) on morphological and biochemical indices 7-16

TABLES (continued)

Number **Page**

7-5 Effects of acid aerosols on individuals with existing disease or illness 7-19

7-6 Mortality effects of acid aerosols 7-21

FIGURES

Number Page

2-1 Solubility diagram for the H^+-NH_4^+-$SO_4{}^{2-}$-H_2O system at equilibrium (30°C) 2-6

2-2 Plot of daily (24-hour) dichotomous fine fraction sulfate and thermal analysis-flame photometric detection (FA-FPD) particulate sulfur (Watertown, MA) 2-8

2-3 Particle size distributions of H^+ and $SO_4^=$ at the tower on Allegheny Mountain, 2000 EDT 24 July to 0800 EDT 11 August, 1977 2-9

2-4 Log probability plot of H^+, NH_4^+ size distribution at the tower on Allegheny Mountain, August 12-17, 19-22, and 28 ... 2-10

2-5a Aerosol mass distribution, Pasadena, CA Dec. 26, 1978 2-11

2-5b Aerosol sulfur mass distribution, Trona, CA, May 13, 1978, from 0946-1145 PDT 2-11

2-6 Annual average N-NH_4^+ emissions from cattle and hogs 2-18

2-7 Annual average N-NH_4^+ emissions from humans 2-19

2-8 Annual average N-NH_4^+ emissions from cattle, hogs, humans, and fertilizer 2-20

2-9 Scatter diagram of sulfate to ammonium mass concentration ratios as a function of sulfate concentration for high volume filter samples 2-21

2-10 Distribution of SO_2 emissions in the SURE area for summer (metric tons/day). Emissions are based on data representative of 1977 2-26

2-11 Distribution of NO_x emissions in the SURE area for summer (metric tons/day). Emissions are based on data representative of 1977 2-27

2-12 Monthly average distribution of 24-hour HIVOL particulate sulfate concentrations in the eastern United States 2-28

2-13 Geographical distribution of the ratio of sulfate to total airborne sulfur for different seasonal periods (in percent) 2-30

2-14 Historical London daily aerosol acidity data. (Total H^+ as sulfuric acid) 2-32

FIGURES

Number Page

2-15 6-hour $SO_4^=$ and H^+, and 6-hour maximum O_3 samples collected during August, 1977 at High Point, NJ 2-48

2-16 Nitric acid measurements taken at Claremont, CA, 1979 2-58

2-17 Diurnal variation in nitrate concentration, Raleigh, NC, 1985 2-61

3-1 Deposition efficiency (percentage deposition of amount inhaled) in humans and experimental animals for total respiratory tract 3-4

3-2 Deposition efficiency (percentage deposition of amount inhaled) in humans and experimental animals for upper respiratory tract 3-5

3-3 Deposition efficiency (percentage deposition of amount inhaled) in humans and experimental animals for tracheobronchial region 3-6

3-4 Deposition efficiency (percentage deposition of amount inhaled) in humans and experimental animals for pulmonary region 3-7

5-1 Mean percent change in specific airway conductance (SGaw) produced by a 16-minute inhalation of sulfate aerosols by asthmatics 5-22

5-2 Change in FEV_1 in asthmatics exposed to various concentrations and particle sizes of sulfuric acid aerosol 5-30

5-3 Effect of H_2SO_4 aerosol exposure on group mean tracheobronchial mucociliary retention of ^{99m}Tc-labelled Fe_2O_3 particles. A. The response of ten healthy subjects who inhaled a 7.6 μm Fe_2O_3 aerosol before a 1 h H_2SO_4 aerosol exposure. B. The response of eight healthy subjects who inhaled a 4.2 μm Fe_2O_3 aerosol before a 1 h H_2SO_4 aerosol exposure 5-33

5-4 Clearance half-time (i.e., time required to clean half the deposited tracer aerosol) as a function of the concentration of acid aerosol to which the subjects were exposed 5-37

6-1 Bronchitis in the last year, children 10-12 years of age in six U.S. cities, by PM_{15} 6-17

6-2 Bronchitis in the last year, children 10-12 years of age in four U.S. cities, by hydrogen ion concentrations 6-17

ABSTRACT

This report evaluates scientific information on direct health effects associated with exposure to acid aerosols. Although the literature up to 1987 has been reviewed thoroughly for information relevant to acid aerosols, the present report is not intended as a complete and detailed review of all literature pertaining to acid aerosols. Rather, an attempt has been made to focus on the evaluation of those studies providing key information on health effects and aerometrics. This report includes discussion of: the physical and chemical properties of acid aerosols; ambient monitoring techniques and ambient concentrations; the toxicology of acid aerosols in experimental animals, including a discussion of information on deposition and neutralization of acid aerosols; assessment of epidemiological studies of health effects of acid aerosols; assessment of controlled human exposure studies evaluating the effects of acid aerosols; and a summarization of the above information with appropriate interpretations and conclusions. Lastly, important research needs are identified which are critical to be addressed in order to improve the data base for acid aerosols and associated health effects as a basis for decisions on whether to list acid aerosols as a criteria pollutant for development of criteria and national ambient air quality standards.

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1. INTRODUCTION

The United States Clean Air Act and its 1977 Amendments require the U. S. Environmental Protection Agency (U.S. EPA) to periodically review criteria for National Ambient Air Quality Standards (NAAQS) and NAAQS themselves, and to revise such criteria and standards as appropriate. This process led to the publication in 1982 of the EPA document Air Quality Criteria for Particulate Matter and Sulfur Oxides and an addendum to that criteria document addressing further information on health effects. Subsequently, a second addendum to the criteria document that updated the earlier document by evaluating new studies and their implications for determination of health-related criteria for the PM and SO_2 NAAQS was published in 1986. In this process of reviewing new scientific studies concerning health effects of PM and SO_2, it became apparent that researchers had identified acid aerosols as one constituent of the PM/SO_2 airborne mix that may be associated with observed PM/SO_2 health effects. The Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board, accordingly, recommended that an acid aerosol issue paper be prepared to evaluate newly emerging literature concerning health effects directly associated with acid aerosols and to address the issue of possible listing of acid aerosols as a separate criteria pollutant for regulation by means of National Ambient Air Quality Standards. To this end, the present report provides a concise review of the most relevant information to characterize ambient concentration patterns and human exposures as well as possible acute and chronic health effects of acid aerosols derived from available animal, controlled human, and epidemiological studies. Considerations for the possible listing of acid aerosols as a criteria pollutant are also presented. The report concludes by highlighting research needs.

Atmospheric aerosols consist of two principal components: a gas phase ("air") and a solid or liquid particle phase in suspension. The discussion in this document focuses on the major strong acid species that contribute to aerosol acidity, primarily strong acid sulfates (particles at typical ambient conditions) and to, a lesser extent, nitric acid (a vapor at typical ambient conditions) and other acidic species.

Strong acid sulfates - sulfuric acid (H_2SO_4) and ammonium bisulfate (NH_4HSO_4) - appear to be the main species of concern in ambient acid aerosols and are the most studied species. Sulfuric acid in particular has been the focus of many of the available studies, both in terms of ambient measurements and health effects research. However, other acid species, especially nitric acid, may be of concern in certain exposure situations, such as the acid fogs of western coastal cities, or may influence neutralization reactions and thus total aerosol acidity. Nitric acid is completely scavenged to droplets in fogs. Weak acids may also be present in the atmosphere, but these have not been measured in conjunction with strong acid aerosol at ground base monitors.

Only limited data are available by which to characterize acid aerosols and their concentrations in ambient air. Chapter 2 of this document discusses the available information on this subject and possible human exposures as well. The chapter first examines the chemical and physical properties of acid aerosols, meteorology, emission densities and distribution of the major species contributing to atmospheric acidity, and historic acid levels. Following that discussion, another section examines the various measurement methodologies and the final section of the chapter examines recent data on atmospheric concentrations and "events."

Chapter 3 examines the deposition and fate of inhaled acid aerosols in the respiratory tract. Important concepts discussed include hygroscopic growth and neutralization by airway secretions or absorbed ammonia.

Chapters 4, 5, and 6 examine the available health effects information for acid aerosols. The bulk of the animal and controlled human studies involve acid sulfates, primarily submicrometer H_2SO_4. There are no animal data, and limited controlled human exposure data, for larger droplets that would be typical of acid fogs. Few data are available for nonsulfur constituents of acid fogs or other acidic atmospheres, such as nitric acid. Most of the pertinent epidemiological studies do not have direct acid measurements, but are suggestive of human health effects being associated with air pollution exposures where there is good reason to believe that high ambient acid concentrations existed. Only a very limited set of epidemiological studies have either subsequent or concurrent acid measurements.

Chapter 4 discusses the toxicology of acid aerosols in experimental animals. Available studies indicate effects from both acute and chronic exposures. This chapter examines mortality, pulmonary function, respiratory tract morphology and biochemistry, and respiratory tract defenses. The effects of mixtures containing acid aerosols are also reviewed.

Available controlled human exposure studies for acid aerosols are discussed in Chapter 5. These studies have looked at the effects of acute exposure on pulmonary function in both normal and asthmatic subjects and on blood biochemistry. Such studies have also evaluated the effects of mixtures of acids with other pollutant gases or aerosols and pulmonary clearance mechanisms.

Chapter 6 discusses relevant epidemiological studies, including acute effects studies from historical episodes, acute exposure of children, acute exposure to sulfate, and a European acid event of 1985; and chronic effects studies from acid mist exposure in Japan, sulfate and SO_2 exposures, nitrogen oxide exposures, and chronic occupational exposures.

Chapter 7 of this document assesses and integrates the available information by which to address the central question of whether there is sufficient and compelling evidence to proceed with the separate listing of acid aerosols as a criteria air pollutant under Section 108 of the Clean Air Act. The major considerations discussed include: (1) characterizing and defining acid aerosols as a pollutant entity for purposes of regulation and their ambient concentrations; (2) possible health effects of acid aerosols at current ambient levels; and (3) the sources of acid aerosols. Each of these elements is of central relevance for listing decisions under Section 108 of the Act. The final section of this chapter presents alternative courses of action based on the assessment of the available information.

The final chapter of this document (8) presents research needs that reflect deficiencies of the data base identified in Chapters 2 through 6.

2. STRONG ACID AEROSOLS: CHARACTERIZATION AND EXPOSURE

2.1 INTRODUCTION

The information available on the concentration patterns and human exposure to atmospheric acidic aerosol is meager, and many of the available studies were not designed to measure human exposure but rather were part of a program or research directed at characterizing the ambient atmosphere. Nonetheless the information is useful in pointing directions for future work, as well as in estimating the exposure to acidic species for specific conditions. This chapter attempts to summarize the data available on acidic aerosol species with special emphasis on acid sulfate species which represent the major acidic species in ambient acid aerosols and the most studied species to date for both aerometric levels and health effects. Episodic situations are also emphasized. An analysis of historical data accumulated in London, England, during the 1960's is also presented.

Many of the major formation mechanisms for sulfuric acid were previously examined in the Particulate Matter-SO_x Criteria Document (U.S. Environmental Protection Agency, 1982a); therefore, only recent advances and that information necessary for understanding the potential for human exposures will be described. Since there is no reference method for acid sulfate species, another major area of concern is the multitude of techniques that have been used to detect various acid species in the environment. These techniques are summarized along with some discussion of their pertinent strengths and weaknesses. A discussion on nitric acid and related fog processes is also included in the text.

There has been no effort to determine the reliability of the methods used in acid aerosol studies or the uncertainty associated with a particular set of measurements. Almost all studies described have been subject to peer review by journals, indicating a certain degree of confidence in the data. Some of the most recent data which, in some cases, are the most closely associated with actual measurements of exposure, are undergoing peer review and are cited as personal communications.

One important note of caution must be identified for the reader. The detection of acidic sulfur species by the variety of methods described in this chapter has usually resulted in data being available in one of two forms: (1) the compound sulfuric acid or (2) the titratable strong acid hydrogen ion. At present there are no techniques available to detect the intermediate acid species, ammonium bisulfate, although there have been two attempts to infer the ammonium bisulfate concentration when hydrogen ion and sulfuric acid measurements were made simultaneously (Morandi et al., 1983, Lioy and Lippmann, 1986). To place the results from each of the other studies in a context, in each case where only hydrogen ion measurements were measured, the concentrations are expressed as apparent sulfuric acid. Thus the values are probably an over estimate of the actual sulfuric acid concentration since in both urban and rural areas sulfate is usually in a partially neutralized form. Weak acids may also be present in the atmosphere, but these have not been measured in conjunction with strong acid aerosol at ground based monitors.

2.2 CHEMICAL AND PHYSICAL PROPERTIES OF ACID AEROSOLS

2.2.1 Formation of Acid Sulfates

The mechanisms involved in the transformation of SO_2 were reviewed in the Particulate Matter and Sulfur Oxides Criteria Document (U.S. Environmental Protection Agency, 1982a), and are listed with the reaction rates listed in Table 2-1. Included are both heterogeneous and homogeneous reactions which produce H_2SO_4 in the gas phase or within the aqueous phase. Additional potential mechanisms involve metal catalysts, carbon, and surface reactions. The reaction rates in the atmosphere range from <0.5 percent to >100 percent per hour. Some of the values have a greater degree of confidence associated with them than others. Although it is not readily apparent from the table, not all these reactions will occur at the same time. Rather each will be associated with particular environmental conditions either near a source, in a plume, or in the general atmosphere. The importance of a particular reaction scheme will depend on the season, geographic location, time of day (night or daylight) and local or prevailing meteorology.

As one example, Gillani et al. (1981) and Gillani et al. (1983) have studied the oxidation of SO_2 in actual power plant plumes, and the conversions were parameterized for relative humidities (RH) <75 percent and >75 percent.

TABLE 2-1. IMPORTANT REACTION RATES FOR OXIDATION OF SULFUR DIOXIDE

Reaction	Rate, Percent h^{-1}			Comments*
I. Gas Phase				
HO radical	0.3 - 1.3			a
HO_2 radical	0.4 - 2.0			a,b
CH_3O_2 radical	0.3 - 1.5			a,b
II. Aqueous Phase, pH	1	3	5	
Mn (II) catalysis	1E-1	1E+1	1E+3	b,c,d,i
Fe (III) catalysis	5E-5	5E-1	5E+3	c,e,i
C (soot) catalysis	3E+1	3E+1	3E+1	f,i
O_3 (40 ppb)	2E-8	2E-6	2E-4	c,g
O_3 (120 ppb)	6E-8	6E-6	6E-4	c,g
H_2O_2 (1 ppb)	2E-2	3E-2	3E-2	c,h
H_2O_2 (10 ppb)	2E-1	2E-1	3E-1	c,h

Note: "E" denotes "exponent to the base 10" (e.g., 3E-1 = 3×10^{-1}).

*Comments:

a. Typical range for daytime at northern midlatitudes during the summer.

b. This reaction rate is not well established.

c. Assumed that liquid water volume of aerosol = 50×10^{-12} m^3/m^3, (SO_2) = 10 ppb.

d. Assumed that Mn (II) mass concentration = 20 ng/m^3; also, the Mn (II) is assumed to be uniformly dissolved in the liquid water of the aerosol ([Mn (II)] = 8.9×10^{-3} M). Rate calculation used the expression of Neytzell-de Wilde and Taverner (1958).

e. Assumed that Fe (III) mass concentration = 2 $\mu g/m^3$; also, the Fe (III) is assumed to be uniformly dissolved in the liquid water of the aerosol ([Fe (III)] = 0.9 M). Rate calculation used the expression of Neytzell-de Wilde and Taverner (1958).

f. Assumed that C mass concentration = 10 $\mu g/m^3$ and behaves as the soots studied by Chang et al. (1979), whose expression was used for this calculation.

g. Rate calculation was based on Equation 2-39, in criteria document (U.S. Environmental Protection Agency, 1982a).

h. Rate calculation was based on Equation 2-43, in criteria document (U.S. Environmental Protection Agency, 1982a).

i. Influence of inhibitors has been ignored, but they are likely tc suppress the rate by orders of magnitude.

Source: Adapted from the U.S. Environmental Protection Agency Air Quality Criteria for Particulate Matter and Sulfur Oxides (1982).

For the <75 percent conditions, empirical relationships derived from the measurements indicated that the most significant indicator variables were ozone concentration, solar radiation, and plume size. In contrast, for RH >75 percent, the interaction of a plume with clouds significantly enhanced the conversion of SO_2 to particulate sulfur. Each of these processes will contribute to the regional levels of acidic sulfate. The basis for significant accumulations of acid sulfate would be summertime photochemical smog for the former (RH <75 percent) and the presence of a persistent cloud cover or expanding (contracting) cumulus clouds during fair weather for the latter (RH >75 percent).

Recently, Jacob et al. (1984) compared field data collected by five groups on aqueous phase transformations of SO_2. Depending on local conditions, the rates can vary widely (Table 2-2). In a discussion by Schwartz and Newman (1983), the rates in Table 2-2 from Hegg and Hobbs (1981, 1982) were criticized on the basis of the method of calculation. However, the general results from the Jacobs et al. (1984) analyses indicate a need to continue research on aqueous phase reactions since at present the rates of reaction can range from <1 percent to >100 percent/h. The application of particular aqueous SO_2 oxidation mechanisms for particular locations and times of the day requires further research.

TABLE 2-2. AQUEOUS SO_2 OXIDATION RATES IN THE ATMOSPHERE

Location	K (Percent h^{-1})*	Reference
Western Washington (wave clouds)	0 - 300	Hegg and Hobbs (1981)
Western Washington (clouds)	0-600 ± 1,000-1,900 ± 1,900	Hegg and Hobbs (1982)
Los Angeles (aerosol, summer)	6.0	Cass (1981)
Los Angeles (aerosol, winter)	2.0	Cass (1981)
Bakersfield (fogs)	0.9 ± 5.5	Jacob et al. (1984)

*K is a pseudo first-order rate constant expressing sulfate production as a percent of $[SO_2(g)]$.

Source: Adapted from Jacob et al. (1984).

The particles with diameters less than approximately 2.5 μm contain most of the SO_4^{-2},H^+, and NH_4^+, and these particles will interact more strongly with H_2O vapor. The most important sulfate components are those of H_2SO_4, NH_4HSO_4 and $(NH_4)_2SO_4$. Most aqueous systems contain H^+, NH_4^+, SO_4^{-2}, NO_3^- and Cl^- and these species are usually present in sufficient mass to influence the liquid water concentration and the phase transition points of particles as a function of relative humidity. Presently, phase diagrams for this multicomponent system are not available for conditions relevant for tropospheric particles. However, from the Criteria Document (U.S. Environmental Protection Agency, 1982a) the phase diagram for the H^+-NH_4^+-SO_4^{-2}-H_2O system at equilibrium is shown in Figure 2-1. In this diagram, the dry pure crystals of $(NH_4)_2SO_4$, letovicite $(NH_4)_3H(SO_4)_2$ and $(NH_4)HSO_4$ are indicated as points A, B, and C, respectively. If $(NH_4)_3H(SO_4)_2$, is exposed to relative humidities starting at 0 and increasing to 100 percent, its behavior can be described in terms of the locus BO in Figure 2-1. From 0 percent relative humidity the salt immediately enters the 3-phase zone consisting of $(NH_4)_3H(SO_4)_2$, $(NH_4)_2SO_4$ and some liquid solution of H^+, NH_4^+ and SO_4^{-2}. At point D, the locus intersects a phase boundary for $(NH_4)_3H(SO_4)_2$ and a partial deliquescence occurs. Between point D and the intersection with curve EE_1, solid $(NH_4)_2SO_4$ remains; however, at the intersection of EE_1, a second and complete deliquescence occurs. From EE_1 to point O, only the solution phase is present. In similar fashion, equilibrium paths for salts subjected to various compositions and relative humidities can be traced. The locus EE_2 demonstrates the dependence of the complete deliquescence point relative humidity on the weight percent of H_2SO_4. As the system's acid composition changes from 0 to 35 percent, the complete deliquescence point relative humidity changes from 80 to 39 percent. Thus, NH_3 plays a key role in governing the phase transition points.

The H_2SO_4, $(NH_4)H(SO_4)$, $(NH_4)_3H(SO_4)_2$ and $(NH_4)_2SO_4$ particle systems have been characterized by Charlson et al. (1978), Tang (1976), Tang and Munkelwitz (1977), and Tang (1980). Charlson et al. (1978) used an apparatus that measured the light scattering coefficient of the aerosol as a function of the relative humidity. They obtained good agreement between theory and experiment in observing the hygroscopic behavior of H_2SO_4. However, they observed no deliquescence point for NH_4HSO_4 particles, and one at 38 percent r.h. for $(NH_4)_3H(SO_4)$ particles. Further details are discussed in the Criteria Document (U.S. Environmental Protection Agency, 1982a).

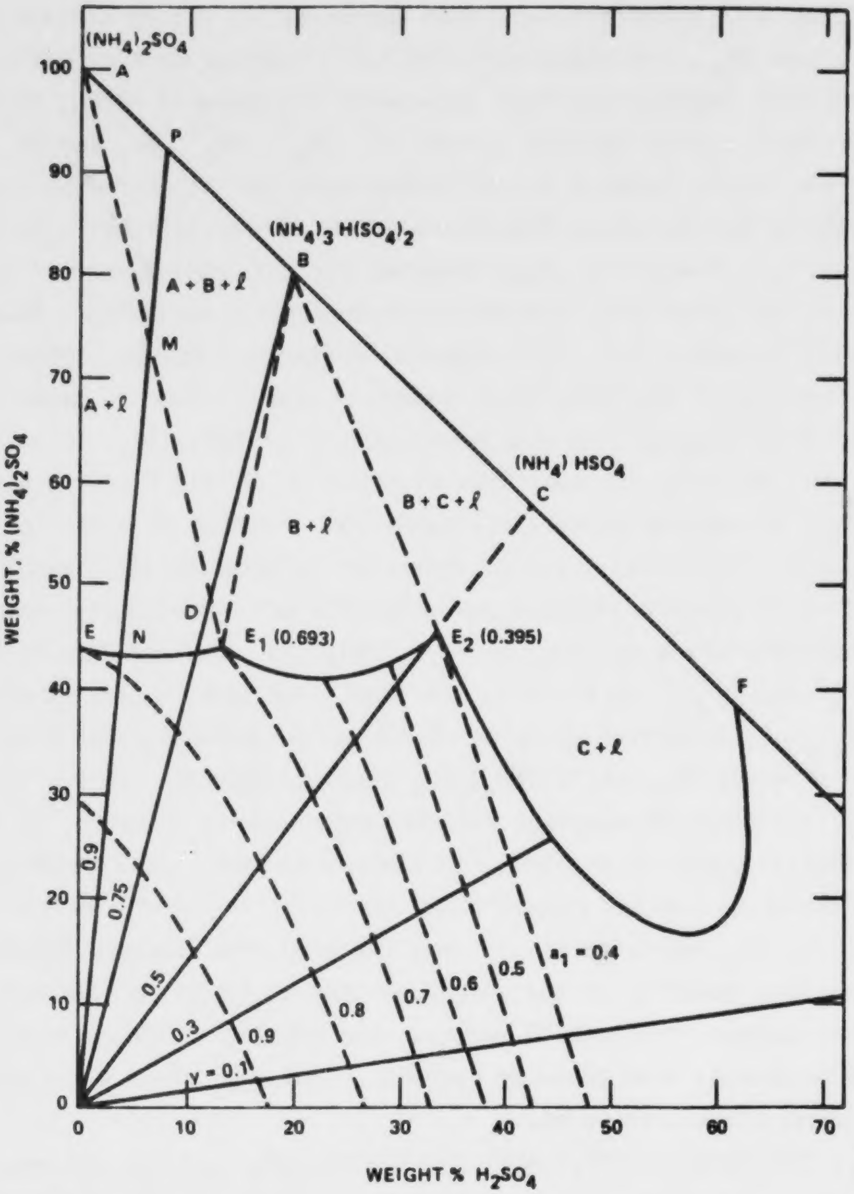


Figure 2-1. Solubility diagram for the $H^+-NH_4^+-SO_4^{2-}-H_2O$ system at equilibrium (30°C).

A = solid phase of $(NH_4)_2SO_4$
B = solid phase of $(NH_4)_3H(SO_4)_2$
C = solid phase of $(NH_4)HSO_4$
ℓ = liquid solution phase
a_1 = fractional relative humidity
y = mole fraction of $(NH_4)_2SO_4$

The numbers in parentheses are the fractional relative humidities for the complete deliquescence points that are indicated.

Source: Tang (1980).

2.2.2 Particle Size of SO_4^{-2} and H^+

Sulfate is in the fine particle size range (<2.5 µm) and is in the acidic fraction of the atmospheric aerosol as shown in Table 2-3. A very good example of the correspondence that can be observed between the fine particulate mass and the SO_4^{-2} ion is shown in Figure 2-2, which shows data from Watertown, MA, a suburb of Boston during the summer of 1984 (Spengler et al., 1986).

The seasonal and annual size segregation results from the nine Class I Sulfate Regional Experiment (SURE) sites located in the Eastern U.S. from 1977 through 1987 show that 80 percent of the SO_4^{-2} is in the fine particulate range (Mueller and Hidy, 1983). The percentage varied from 50 to 100 percent, depending upon the site and the month of the year with the lowest percentages occurring in the fall and the winter.

Size distribution data have been acquired for sulfate and hydrogen ion by Pierson et al. (1980b) and Keeler (1987) in two separate investigations at Allegheny Mt., PA during July and August of 1977, and August in 1983. The cumulative mass equivalent size distributions for the respective studies are shown in Figures 2-3 and 2-4. The mass median equivalent diameters were 0.84 µm and 0.7 µm for both H^+ and SO_4^{-2}. Since these data were taken in the Eastern U.S., the potential for having high relative humidity in the summer would increase the particle size of the sulfate species above that found initially by gas-phase or liquid-phase reactions. In the 1977 study the average relative humidity was 79 percent and the average nighttime relative humidity was 91 percent.

In California, two types of sulfur particle mass size distributions have been noted and each is illustrated in Figure 2-5 (Friedlander, 1980). The Pasadena, CA sulfate distribution in Figure 2-5 (top) appears to be similar to that observed by Pierson et al. (1980b) and Keeler (1987) with most of the mass found centered around 0.5 µm. Friedlander has classified this as a coastal sulfur aerosol (multiply by 3 to approximate sulfate mass). The distribution shown in Figure 2-5 (bottom) shows the sulfur mass having a mode which is shifted down to between 0.1 and 0.2 µm. This was classified as desert type sulfur aerosol that appeared to be formed from homogeneous reaction mechanisms but did not grow appreciably in the arid atmosphere. The concentration of the desert sulfate aerosol was less than 2.0 µg/m^3. This could have contributed to the smaller sizes since there would have been less coagulation of particles in dispersed conditions. No information on the distribution of aerosol acidity

TABLE 2-3. CLASSIFICATION OF MAJOR CHEMICAL SPECIES ASSOCIATED WITH ATMOSPHERIC PARTICLES

Fine Fraction	Coarse Fraction	Both Fine and Coarse Fractions	Variable
SO_4^{-2}, C (soot)	Fe, Ca, Ti, Mg	NO_3^-, Cl^-	Zn, Cu, Ni, Mn
Organic (condensed vapors)	K, PO_4^{-3}, Si, Al Organic (pollen, spores, plant parts)		Sn, Cd, V, Sb
Pb, NH_4^+, As			
Se, H^+, acids	Bases		

Source: Air Quality Criteria for Particulate Matter and Sulfur Oxides (U.S. Environmental Protection Agency, 1982a).

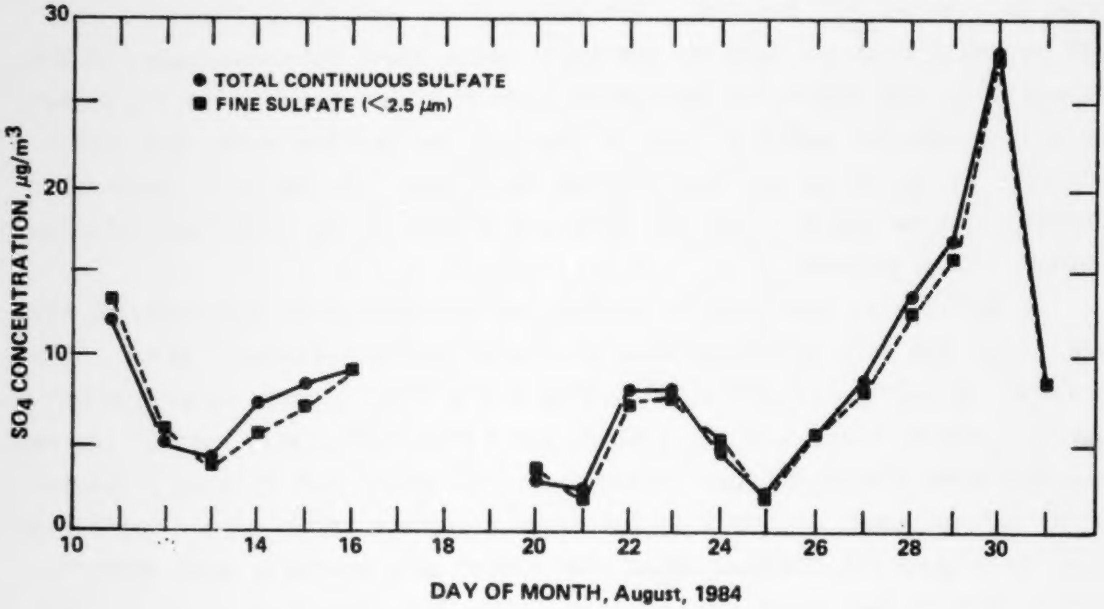


Figure 2-2. Plot of daily (24-hour) dichotomous fine fraction sulfate and thermal analysis-flame photometric detection (TA-FPD) particulate sulfur (Watertown, MA).

Source: Spengler et al. (1986).

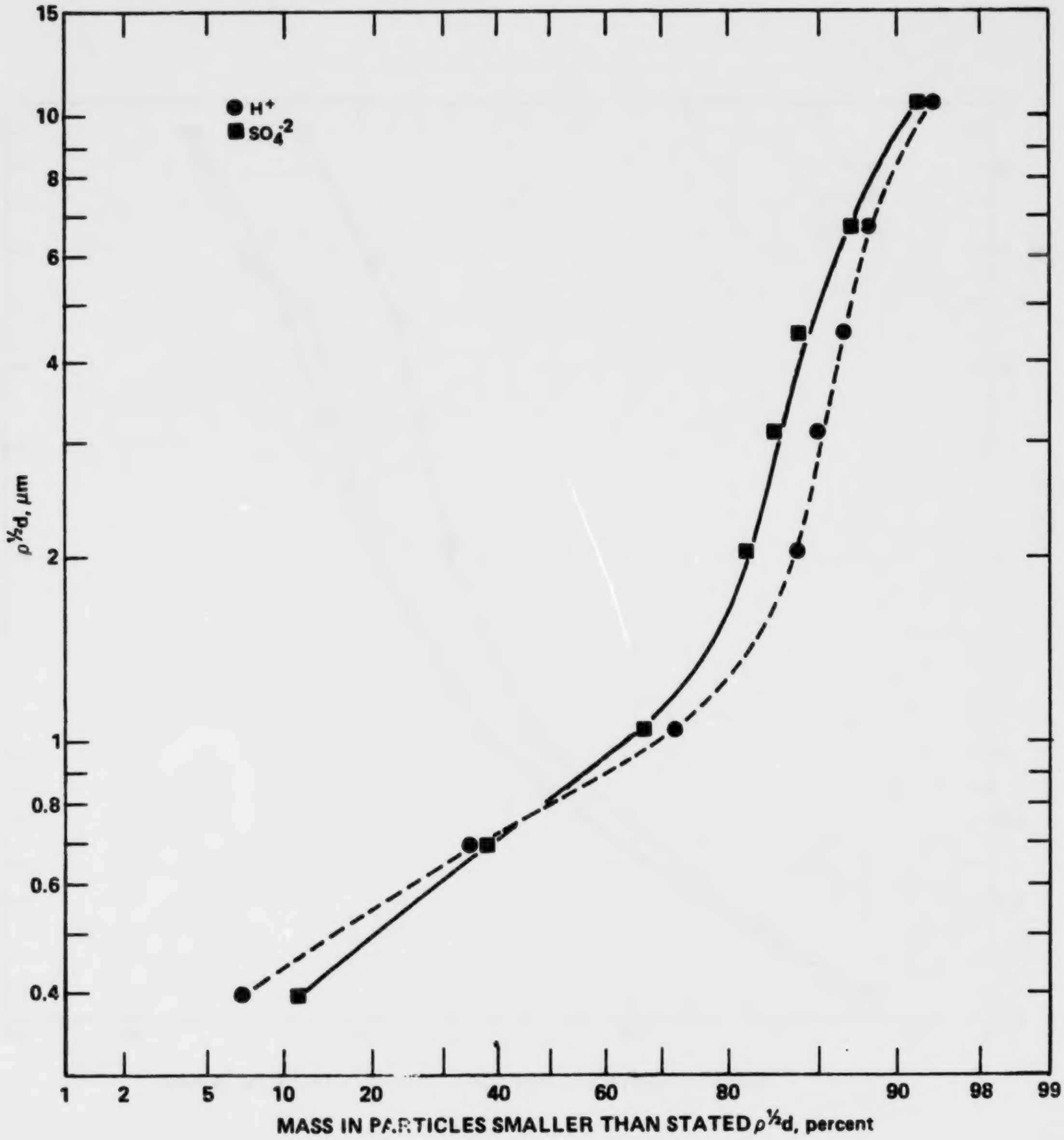


Figure 2-3. Particle size distributions of H^+ and $SO_4^=$ at the tower on Allegheny Mountain, 2000 EDT 24 July to 0800 EDT 11 August, 1977.

Source: Pierson et al. (1980b).

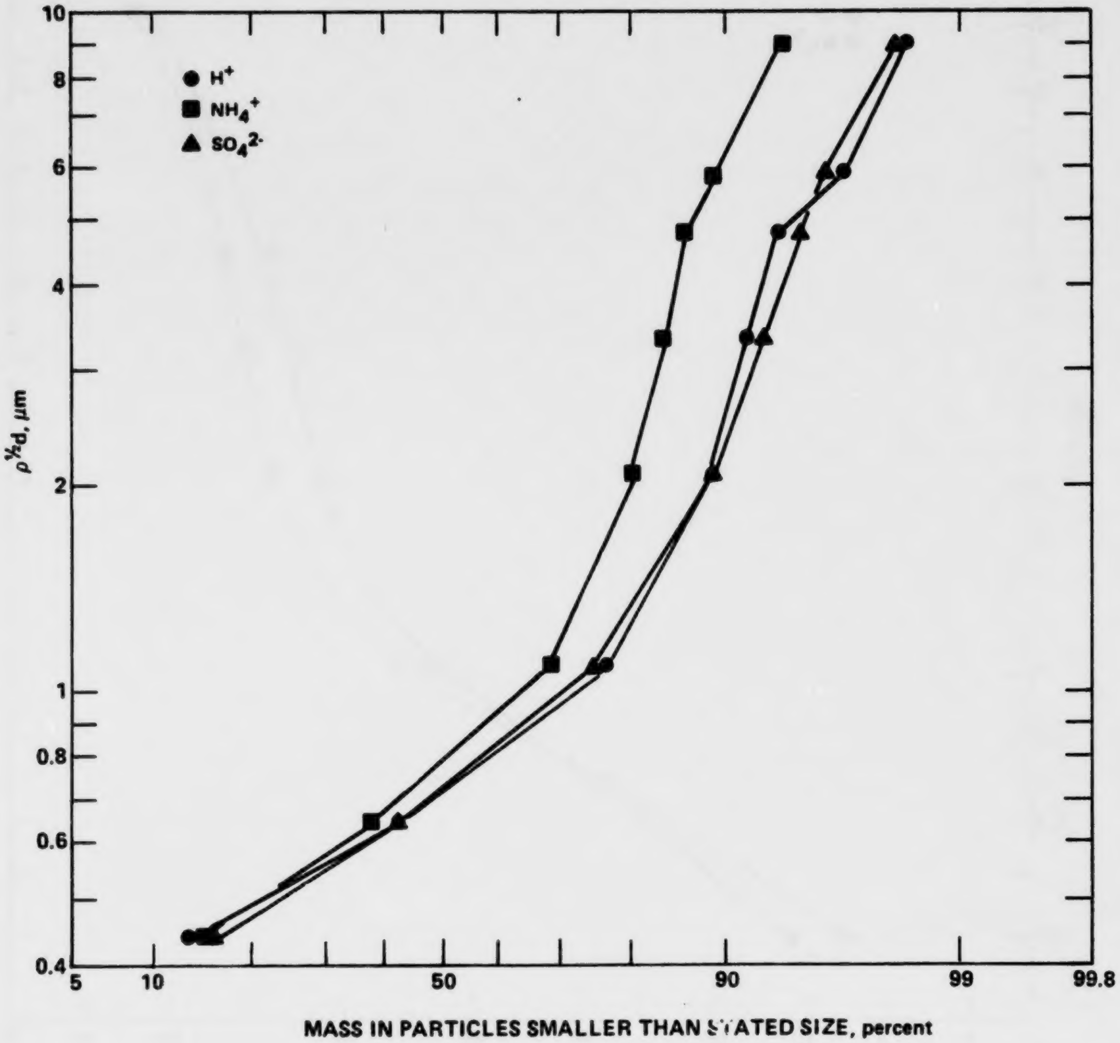


Figure 2-4. Log probability plot of H^+, NH_4^+, and SO_4^{2-} size distribution at the tower on Allegheny Mountain, August 12-17, 19-22, and 28.

Source: Keeler (1987).

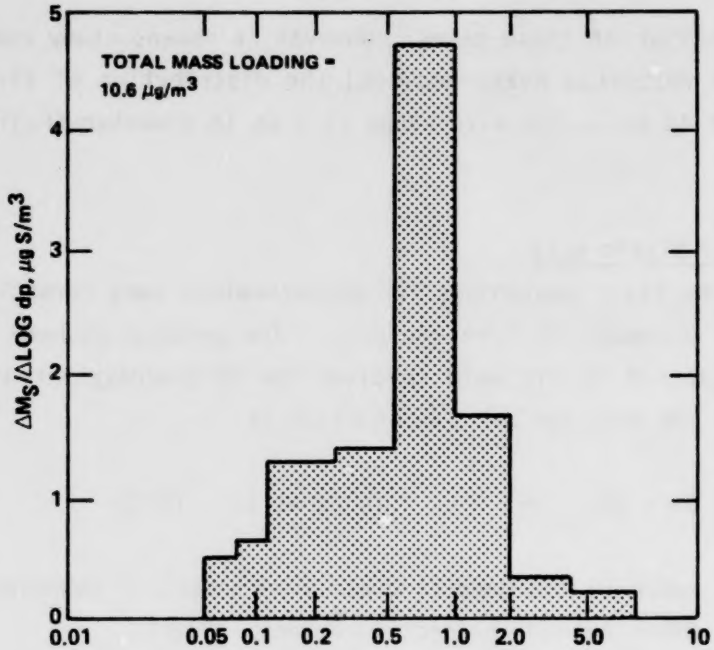


Figure 2-5a. Aerosol mass distribution, Pasadena, CA, Dec. 26, 1978. Average of two samples from 1428-1600 PST.

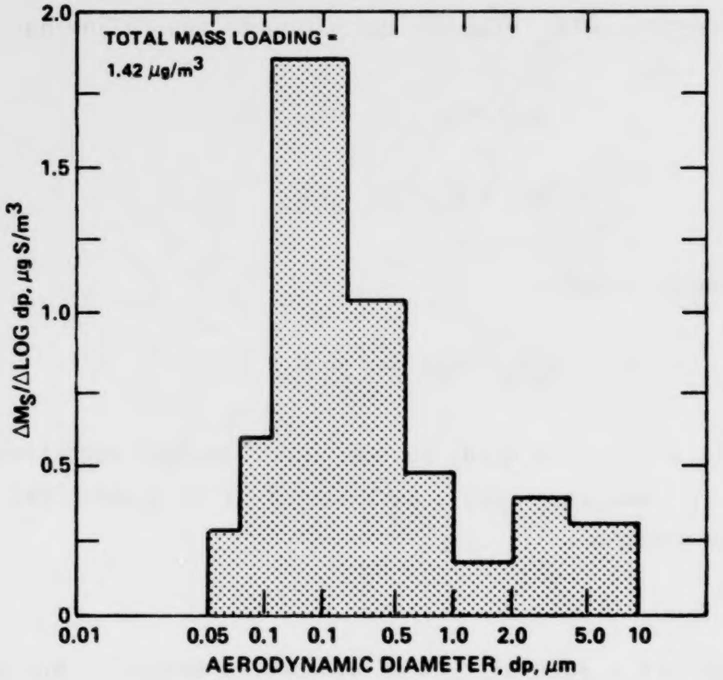


Figure 2-5b. Aerosol sulfur mass distribution, Trona, CA, May 13, 1978, from 0946-1145 PDT.

Source: Freidlander (1980).

was available in either of these cases. However, a recent study conducted by the California Air Resources Board measured the distribution of strong acid found and found it to be in the size range <1.5 µm in diameter (Fujita et al., 1986).

2.2.3 Formation of Nitric Acid

Formation. The basic mechanisms for photochemical smog formation include the production of a number of free radicals. The primary pathway for the atmospheric formation of nitric acid involves the OH (hydroxyl) radical which is produced within the smog cycle. The reaction is:

$$OH + NO_2 \longrightarrow HNO_3 \quad \text{(Tsang et al., 1977)}$$

This reaction can occur in the general urban environment or downwind of power plant plumes (U.S. Environmental Protection Agency, 1982b).

Another possible mechanism for the formation of nitric acid involves the reaction of dinitrogen pentoxide (N_2O_5) with water. The formation of N_2O_5 results from the reaction of O_3 with NO_2 according to the following:

$$O_3 + NO_2 \longrightarrow NO_3 + O_2$$

$$NO_3 + NO_2 \longrightarrow N_2O_5$$

then in the presence of water:

$$N_2O_5 + H_2O \longrightarrow 2HNO_3$$

Nitric acid is a volatile acid, so that under ambient conditions it is a vapor. The vapor will coalesce into a particle if it is neutralized by ammonia to produce ammonium nitrate salt.

2.2.4 Acid Fogs

Fog and clouds are a special type of atmosphere aerosol. While aerosols are generally composed of crystalline, aquated salt, or other solid particles, fogs and clouds are the suspension of liquid water droplets in the air. Such droplets form by condensation of water vapor on preexisting fine aerosol particles called condensation nuclei. However, this occurs only when the atmosphere is saturated with water vapor (i.e., relative humidity >100 percent).

From nuclei of 0.1 to 1.0 µm, droplets grow to diameters between 2 to 100 µm, although the majority of droplet mass occurs in the range of 5 to 30 µm. In contrast, raindrops are in the range of 200 to 2,000 µm. In fogs and clouds, the mass of liquid water is typically 0.01 to 0.5 g/m^3; the number concentration of droplets is generally 10 to several $100/cm^3$.

The presence of condensation nuclei, composed of both soluble and nonsoluble material, is essential to the formation of atmospheric water droplets. The effects of surface tension and the chemical potential of the aquated solutes are important; these raise and lower the saturation vapor pressure near the droplet surface, respectively. Accretion or evaporation of water to the condensation nucleus or droplet is forced by the difference between the ambient and local (i.e., surface) humidities. Droplet growth equations have been derived by coupling microscale heat and mass transfer at the aerosol surface. The principal terms depend on: (a) atmospheric relative humidity; (b) droplet surface tension; and (c) solute activity.

In many respects, fog is simply a ground-level cloud in which processes such as nucleation, gas scavenging, and droplet growth are important. At the same time, fogs consist of discrete water droplets, and sedimentation and inertial impaction are dominant transport mechanisms due to the relatively large sizes of these particles. However, since fog droplets may change size continually, their transport behavior may be altered.

Fog droplets are highly effective at scavenging pollutant materials present in the air. The overall fraction incorporated into fog droplets depends upon two processes: nucleation scavenging (i.e., activation) of aerosol and gas dissolution. The speciation of pollutant components present prior to fog formation is therefore important. Furthermore, *in situ* chemical transformations (e.g., oxidation of SO_2 to sulfuric acid) may alter this speciation and the effectiveness of fog scavenging while the droplet phase is present.

The pollutant species of concern are often present as hygroscopic aerosol (e.g., ammonium sulfate and ammonium nitrate). These will deliquesce to form aquated condensation nuclei at high relative humidity (RH), growing to larger equilibrium sizes as RH approaches 100 percent. Under droplet-forming conditions, the larger and more soluble aerosol grow into droplets first; however, these relationships are at best qualitative. This area of fog microphysics, the size-composition relationship within droplet spectra, may strongly affect the chemistry and deposition of fog-borne material. It remains an area in need of further research.

Dissolution of gaseous species in fogwater is dependent on gas-aqueous equilibria and the quantity of liquid water present. Temperature and pH are the most important parameters that affect phase equilibria (e.g., aqueous, gas-aqueous, etc.). Sulfur dioxide is fairly insoluble at low pH. Only at higher pH (7 and above) does dissociation of the gas in solution lead to appreciable SO_2 solubility. In contrast, nitric acid is completely scavenged to droplets for fogs even at minimal liquid water content (LWC).

Under most conditions, the rate of gas transfer to fog-sized droplets by molecular diffusion is sufficiently rapid for phase equilibria to be achieved on the order of seconds or less under most conditions (Baboolal et al., 1981; Schwartz, 1984).

The study of fog has traditionally remained in the domain of atmospheric physicists principally concerned with its effect on visibility or the mechanisms of formation analogous to clouds. Yet, even the data of early investigations of fog indicate that fogwater can be highly concentrated with respect to a variety of chemical components (see Table 2-4). Cloudwater, sampled aloft, has been found with similar composition, although not with the same extreme values. On the other hand, rainwater compositions, when compared to fogwater, are found to be far more dilute. This makes sense, since fog droplets are approximately 100 times smaller than raindrops, which form partially by the further condensation of water vapor. Hence, fog and cloud water should be more concentrated in solute derived from the condensation nuclei. Furthermore, fog forms in the ground layer where gases and aerosol are most concentrated.

The higher aqueous concentrations and extremes in acidity found in fogwater are reason for concern. Fog-derived inputs have the potential to add substantially to the burden of acid deposition caused by precipitation. Its contribution can be disproportional to the sum of additional moisture because of its higher concentrations. Perhaps more important, deleterious effects of fog deposition may be associated with the intensity of solution acidity. For instance, appreciable nutrient leaching (Scherbatskoy and Klein, 1983) and damage to leaf tissue (Haines et al., 1980) have been noted with application of acid fog or mists. An historical correlation of fog with the most severe air pollution episodes provides additional cause for concern (Hoffman, 1984).

TABLE 2-4. SUMMARY OF FOGWATER COMPOSITION MEASUREMENTS

Location	Date	Type$^{(b)}$	N$^{(c)}$	pH	Na^{+}	NH_4^{+}	Ca^{+2}	Mg^{+2}	Cl^{-}	NO_3^{-}	SO_4^{-2}	Reference
Mt. Washington, NH (1,900 m)	1930 - 1940	I	35*	4.5 3.0-5.9					4 0-34		150 4-1,100	Houghton (1955)
Coastal MA & ME	1930 - 1940	M	37*	4.7 3.5-6.3					940 0-5,800		380 60-2,600	
Germany, Baltic Sea	1955 - 1965	M	42*	3.8	1,500	2,300	750		700	900	1,900	Mrose (1966)
nr. Dresden	1955 - 1965	R	12*	4.2		2,100	3,200		590	450	780	
Harz Mountain (1,150 m)	1955 - 1965	I	18*	5.1	300	710	220		200			
Japan, Mt. Noribura (3,026 m)	July 1963	I	10^{+}	3.9 3.4-4.3	87 45-165	175 115-260			110 75-230	36 25-175	3,300 230-1,250	Okita (1968)
Mt. Tsukaba (876 m)	November 1963	I	5^{+}	5.9 5.6-6.5	290 180-435	880 110-965			800 295-1,290	17 5-37	1,600 360-2,100	
Whiteface Mountain, NY (1,500 m)	August 1976	I$^{(d)}$	28*	3.7	11	89	17	6	31	90	140	Castillo et al. (1983)
	August 1980	I	50	3.2-4.0	1-7	1-200			1-14	7-190	32-800	Falconer (1981)
Los Angeles foothills (780 m)	Spring 1982 and 1983	I	120^{+}	2.9 2.1-3.9	240 135-8,700	580 62-7,400	140 5-3,000	80 1-1,800	190 15-9,650	1510 160-16,300	840 130-9,300	Waldman et al. (1985)
Nova Scotia	August 1975	M	14°		1,040 600-1,530	33 3-94	45 20-69	100 13-130	87 3-450		250 50-500	Mack and Katz (1976)
California, Central Coast	Fall 1976	M	8°		320 80-950	190 0-580	55 9-100	68 23-175	400 95-1,240	115 24-235	200 77-490	Mack et al. (1977)
Los Angeles area	Fall-Winter 1980 - 1982	M & I	11^{+}	3.3 2.7-7.1	139 30-620	1,580 420-4,260	168 0-460	54 22-310	223 68-423	110 580-2,980	584 354-1,875	Brewer et al. (1983)
Los Angeles area	Fall-Winter 1981 - 1982	M	24	2.3-5.8	12-2,180	370-7,960	190-4,350	7-1,380	56-1,110	130-12,000	62-5,000	Munger et al. (1983)

(continued on the following page)

TABLE 2-4. (continued)

Location	Date	Type^(b)^	N^(c)^	pH	Na^+	NH_4^+	Ca^{+2}	Mg^{+2}	Cl^-	NO_3^-	SO_4^{-2}	Reference
Pt. Reyes, CA	August 1982	M	17^+	4.5 3.5-5.0	190 21-4,700	64 28-330	10 0-240	36 5-1,200	215 34-7,000	23 2-526	186 36-1,281	Jacob et al. (1985)
San Nicholas Island, CA	August 1982	M	7^x	3.9	6,100	450	450	1,500	5,300	1580	1,080	Jacob et al. (1985)
San Diego Area, CA	January 1983	M	5^x	2.9	510	780	49	130		1,850	470	
Albany, NY	October 1982	R	24^+	5.8 4.3-6.4	36 10-100	215 70-350	120 65-350	13 6-47	47 18-175	85 11-220	155 21-1,360	Fuzzi et al. (1984)
Bakersfield, CA	Winter 1983	R	108^+	4.2 2.6-7.0	20 1-325	1,440 490-1,330	47 7-3,500	6 1-430	47 1-980	850 200-6,800	1160 10-9,400	Jacob et al. (1984)
Italy, Po Valley	February and November 1984	R	5^o	3.5-4.3	10-110	580-1,620	60-130	10-50	20-120	290-1,100	400-990	Fuzzi et al. (1984)

[a] Concentrations in micro-equiv L^{-1}.

[b] Fog type:
I = intercepted stratiform cloud;
M = marine or coastal fog;
R = radiation fog.

[c] Number of samples or events: (*) = average, (+) = median,
(x) = volume-weighted mean of n samples;
(o) = average and/or range of n events.

[d] Nonprecipitating stratiform cloud data only.

Source: Waldman and Hoffmann (1987).

Identification of a link between urban fog events and human injury was made even before detailed measurements of fog composition (Firket, 1936).

2.2.5 Neutralization

A key factor in determining the persistence of atmosphere acid sulfate species is the potential for ammonia neutralization, which is controlled by the reaction of ammonia with sulfuric acid, and the formation of ammonium salts (NH_4HSO_4 and $(NH_4)_2SO_4$). The principal sources of environmental ammonia appear to be animals and humans, although there can also be significant contributions from fertilizer manufacturing. For both animals and humans, the emissions are a result of excretion through the skin or from urea. Animals are probably a much larger source due to the sewage treatment of human excrement. The results of a regional mapping of domestic animal (cattle and pigs) and human ammonium emissions by Husar (1982) are shown in Figures 2-6 and 2-7. The regional distributions are quite different, with the animal ammonium emissions centered in the midwest and the human emissions keyed to the major population centers. Husar and Holloway (1983) also added the emissions inventory for fertilizer production and the final emissions estimates for ammonium are shown in Figure 2-8. These emission estimates suggest that ammonia neutralization will be dependent upon the land areas over which a sulfuric acid-laden air mass travels, and whether the air mass is in contact with the surface.

At present, there are very few measurements of ammonia, but there are data on the NH_4^+ ion, and usually these are linked to measurements of sulfate ion. One comprehensive study of SO_4^{-2} was the Sulfate Regional Experiment (SURE) (Mueller and Hidy, 1983) which included measurements of these two ions for nine sites in the eastern U.S. over a two-year period. The mass ratio of SO_4^{-2}/NH_4^+ was calculated for all sites, and the frequency of occurrence suggested that 40 percent of the samples were a mixture of ammonium salts and 60 percent could have contained free sulfuric acid. A scatter diagram from the SURE (Mueller and Hidy, 1983) of the Hi-Vol mass ratio of SO_4^{-2}/NH_4^+ versus sulfate concentration is shown in Figure 2-9. (Please note that since these data were taken with a high volume sampler, artifact formation could occur, which causes these data to be qualitative.) The distribution of the data suggests that the highest percentage of acid concentrations are probably associated with moderately high sulfate concentrations (<15 $\mu g/m^3$) and not with the extremely high sulfate concentrations that are usually measured during the intense portions

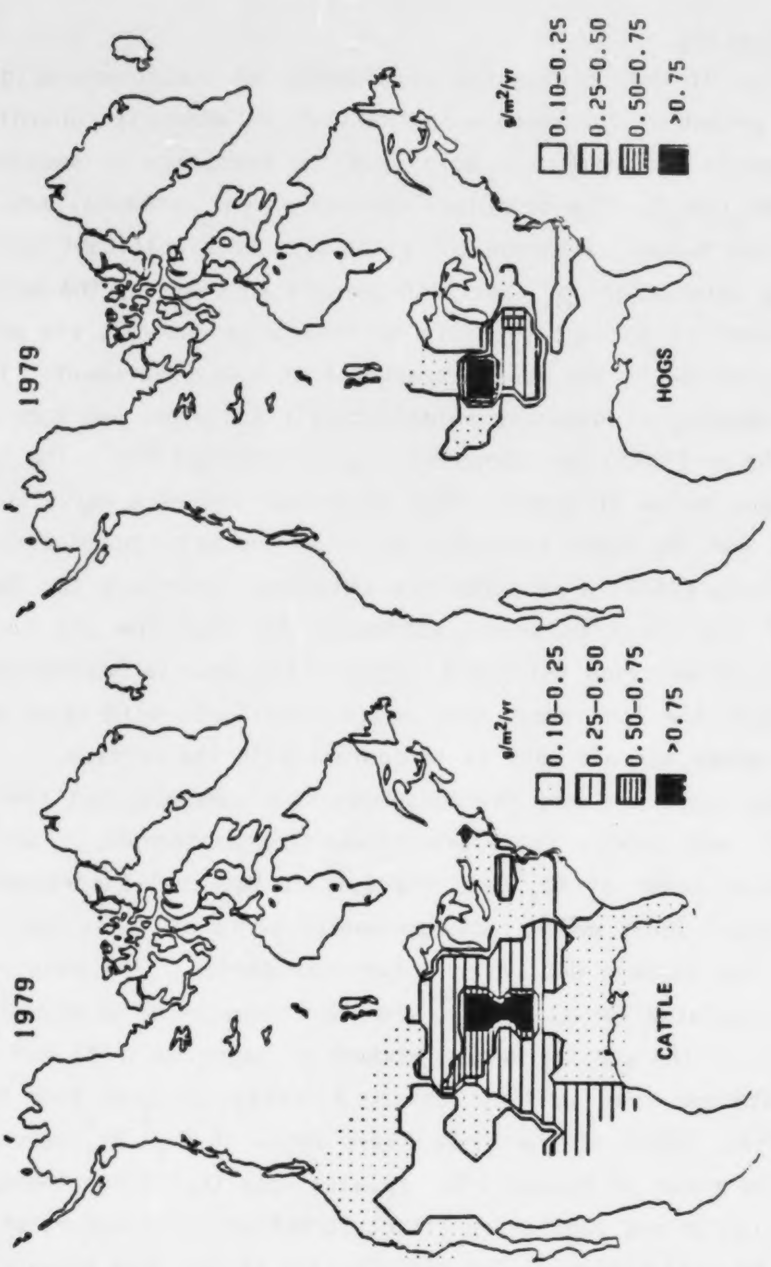

1979
CATTLE
g/m²/yr
0.10–0.25
0.25–0.50
0.50–0.75
>0.75
1979
HOGS
g/m²/yr
0.10–0.25
0.25–0.50
0.50–0.75
>0.75

Figure 2-6. Annual average N−NH_4^+ emissions from cattle and hogs.

Source: Husar (1982).

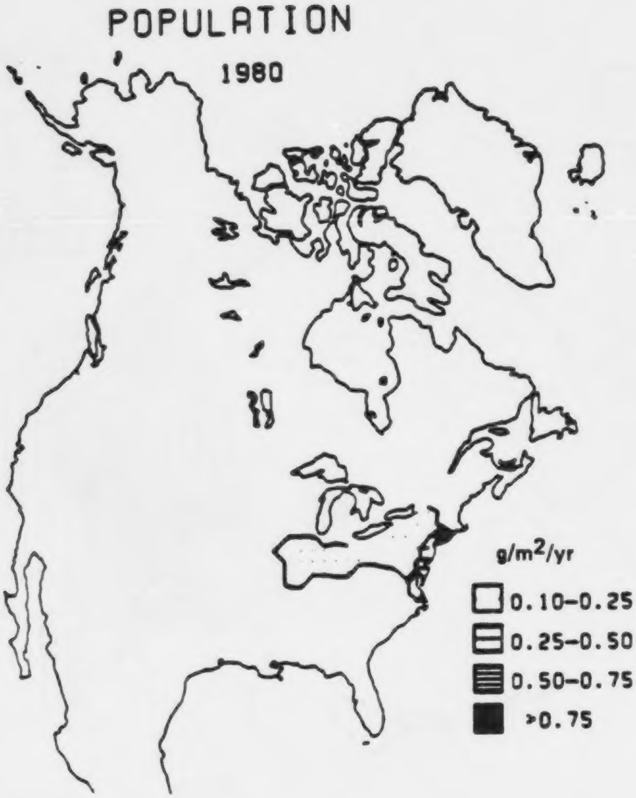

POPULATION
1980
g/m2/yr
0.10–0.25
0.25–0.50
0.50–0.75
>0.75

Figure 2-7. Annual average N—NH$_4^+$ emissions from humans.

Source: Husar (1982).

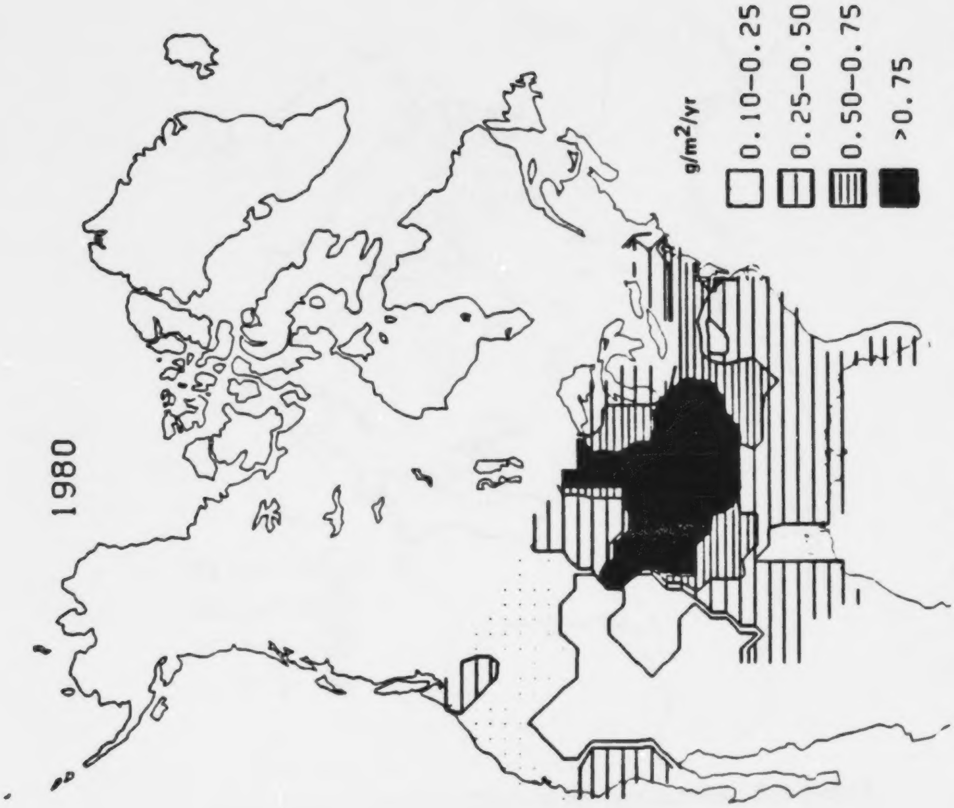

1980
g/m^2/yr
0.10–0.25
0.25–0.50
0.50–0.75
>0.75

Figure 2-8. Annual average N–NH$_4^+$ emissions from cattle, hogs, humans, and fertilizer.

Source: Husar and Holloway (1983).

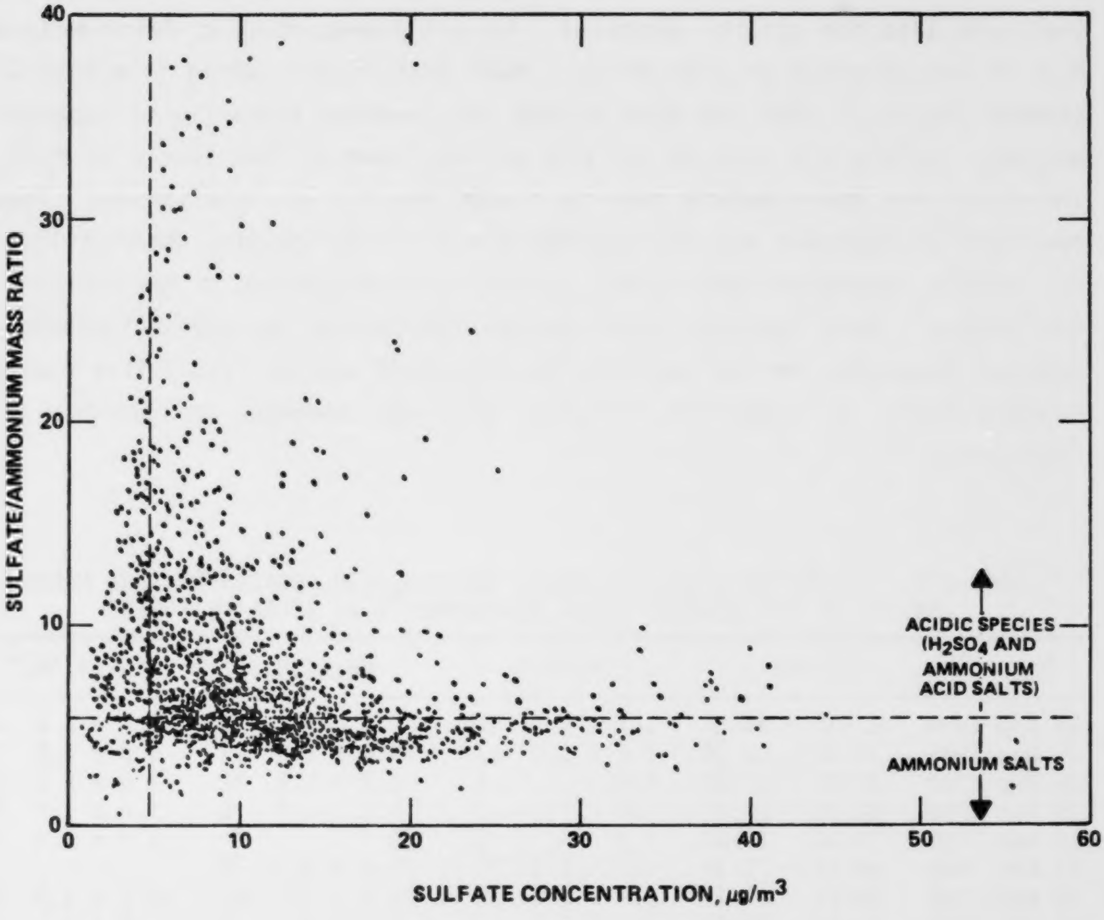


Figure 2-9. Scatter diagram of sulfate to ammonium mass concentration ratios as a function of sulfate concentration for high volume filter samples.

Source: Mueller and Hidy (1983).

of a photochemical smog episode. The preceding does not mean, however, that the acid concentrations cannot reach in excess of 20 μg/m^3.

Studies that have measured strong acid aerosol acidity directly have shown that the highest H^+/SO_4^{-2} ratios will occur at the lowest SO_4^{-2} concentrations (Pierson et al., 1980b; Keeler, 1987; and Morandi et al., 1983). These suggest that the percentage of acid sulfate species is lower with higher SO_4^{-2} since the acid particles have more time to pass over areas with ammonia emissions.

Morandi et al. (1983) examined the local character of the distribution of acid species for a regional smog episode in 1980 (Table 2-5). It can be seen that the most acidic portion of this smog episode occurred at the beginning and that with time the acidity decreased. In a follow-up study at Fairview Lake, N.J. it was observed by Lioy et al. (1987) that in the period from July 31 through August 3, 1984 the acid aerosol was composed primarily of apparent NH_4HSO_4. During the last day of this period, however, the levels of H_2SO_4 increased from approximately zero to 4 μg/m^3 for 4 h in the afternoon. These two types of phenomena must be examined more fully to identify the distribution of possible situations when acidic species could be present in the atmospheric environment. Such research would include identifying the physical-chemical matrices necessary for the accumulation of acidic species (e.g., free radical concentrations in summertime episodes or plume downwash in nocturnal inversions).

TABLE 2-5. ESTIMATED H_2SO_4 $(NH_4)HSO_4$ AND $(NH_4)_2SO_4$ CONCENTRATIONS BASED ON TA-FPD AND QUARTZ FILTER MEASUREMENTS AT STERLING FOREST

Date	Time	H_2SO_4*		$NH_4H(SO_4)$*		$(NH_4)_2SO_4$*	
14 Aug 1980	12:00 - 24:00	1.2 ± 1.0	12†	0.4 ± 0.4	4	8.1 ± 3.1	84
15 Aug 1980	24:00 - 12:00	1.6 ± 1.0	12	1.5 ± 1.0	11	9.9 ± 2.5	77
16 Aug 1980	24:00 - 12:00	0.0	0	1.2 ± 1.0	32	2.6 ± 2.2	68
16 Aug 1980	12:00 - 24:00	0.0	0	0.1 ± 1.0	8	1.0 ± 1.0	92
17 Aug 1980	24:00 - 12:00	0.0	0	0	-	2.9 ± 1.0	90
27 Aug 1980	09:15 - 21:15	5.2 ± 1.3	30	13.4 ± 3.5	70	-	-
28 Aug 1980	09:15 - 21:15	5.4 ± 1.3	19	11.9 ± 3.0	43	10.5 ± 1.5	38
29 Aug 1980	09:15 - 16:05	1.3 ± 1.0	10	1.0 ± 0.9	8	11.0 ± 4.1	82

†As percent of total SO_4^{-2}.

*μmoles of SO_4^{-2} $m^3 \times 10^{-2}$.

Source: Morandi et al. (1983).

2.3 METEOROLOGY

Much has been written in the scientific literature about the development of sulfate events (Hidy et al., 1978; Wolff et al., 1984; Samson, 1980; Dutkiewicz et al., 1983; Lioy et al., 1980; Galvin et al., 1978; Whelpdale, 1978; Rahn and Lowenthal, 1984; Thurston and Lioy, 1987). However, very few studies have addressed the conditions conducive to the formation of local or regional acid sulfate events. The data available on meteorological conditions for acid events will be described for eight of the studies discussed in this chapter, but these should not be considered inclusive, in fact, for the cases reported the meteorological data are very limited. As stated previously, most acid aerosol studies have been conducted during the summertime. Thus, the nature of acidic aerosol events that can occur in different types of locales and during the remaining three seasons must be identified in future chemical characterization and human exposure studies.

In the Kelly et al. (1985) White Mountain, NY study aerosol acidity was closely associated with SO_4^{-2} levels that resulted from the transport of pollutant laden air masses from industrial regions (the air flow was from southerly to westerly directions). The temporal pattern of acid events did not vary with season, however, a seasonal variation of precursor SO_2 and NO_x and the secondary products SO_4^{-2} and HNO_3 was detected. This variation was attributed to seasonal variation in the oxidation process. Homogeneous photochemical oxidation was reduced during the winter months due to decreased temperatures and reduced insolation. Heterogeneous oxidation by H_2O_2 or O_3 in aqueous solution was also reduced due to the low concentration of the oxidants.

In the 1983-1984 Antigonish, Nova Scotia study by Smith-Palmer and Wentzell (1986), acid events were associated with regional plumes that were moved north and east by high pressure systems that passed over the center of the eastern United States and central Canada. No local sources of acid or acid precursors were noted in the analysis. Warm and hazy weather with air mass trajectories over water for long distances characterized the acid events. Air mass trajectories over water minimized the availability of NH_3 from sources on land. Acid aerosol events during the winter were of longer duration but had lower acid levels than summer events. Winter events had high narrow peaks and otherwise low near baseline acid levels.

Pollution events were associated with the transport of pollutants in the Washington, D.C. to New York City corridor in the summer of 1980 study by Morandi et al. (1983). South to southwesterly wind flows appeared to bring regional plumes from the industrial regions of the eastern United States. In the northeast these southwesterly wind flows typically occur during the summer season. Events were associated with slow-moving high pressure systems that accumulated secondary acid sulfate particles in the atmosphere. Decreased visibility due to haze also characterized acid aerosol events.

The Glasgow, Il study by Tanner et al. (1979) showed acid events associated with urban and power plant sources in the St. Louis vicinity. Events occurred during daylight hours and were attributed to homogeneous photochemically induced sulfuric acid formation. Conversely, ammonia levels were higher during the nighttime.

The Lioy et al. (1980) analyses for 1977 found sulfate and acid levels well correlated at High Point, NJ. High sulfate concentrations were associated with westerly winds that carried precursor SO_2 from sources in the Ohio Valley and western Pennsylvania and or the Washington, D.C. to Boston corridor. These occurred with southerly to westerly flow on the backside of high pressure systems that moved slowly across areas of major emissions of SO_2. High ozone levels have also been recorded under these meteorological conditions. High acid was detected in the denser portion of the hazy air mass.

From the year-long investigation in St. Louis (1977-1978) by Cobourn (1979), the summer acid events occurred with haze, stagnation, high temperature, high humidity, and cloudless skies. Elevated surface levels were due to long distance transport of hazy air masses associated with maritime tropical systems. High acid levels during the afternoon hours were attributed to enhanced photochemical gas phase reactions and vigorous mixing of pollutants in the atmosphere.

Winter events occurred with slow moving wind trajectories from the northeast, implicating emissions from the industrial northeastern United States. Recent work by Ferris and Spengler (1985) implicated local plume emissions with the occurrence of high acidic sulfate.

In the St. Louis, MO investigation by Huntzicker et al. (1984) in August, 1979, acid events occurred with a high pressure system characterized by light surface winds from the southwest. In addition, high daytime temperatures and absolute humidity are indicative of a maritime tropical air mass and could also be deficient of ammonia. Two types of events were distinguished: one occurring during the afternoon resulting from gas phase oxidation, and the other early in the evening.

2.4 EMISSION DENSITIES AND DISTRIBUTION

2.4.1 Sulfur and Nitrogen Oxide Emission Densities

In the Eastern half of the United States, sulfur dioxide emissions are highest in the area within the Ohio Valley from the Mississippi River through Southwestern PA, see Figure 2-10. This core area is surrounded with rural and urban centers that have significant SO_2 emissions. In contrast, nitrogen oxide emissions in the east are centered in the metropolitan corridor of New York, New Jersey and Connecticut and the major urban areas such as Chicago and Detroit, see Figure 2-11. The distribution of nitrogen oxide is more uniform throughout the country than is that of sulfur dioxide.

In the western half of the nation, SO_2 emissions are centered in specific areas related to large stationary sources such as smelters. The nitrogen oxides emissions in the west are distributed much more broadly and the actual emission densities are much lower in specific instances.

2.4.2 Sulfate Distribution

Many studies and monitoring programs have routinely provided data on the sulfate ion, which is relatively easy to measure and is a major constituent in the ambient aerosol. Acid sulfate species represent the principal component of most acid aerosols. Thus while the animal toxicology and human clinical studies of this document provide data that strongly suggest that the health effects are related to the hydrogen ion rather than the sulfate ion, sulfate levels should correlate to some degree with acid aerosol levels.

Unfortunately, presence of high sulfate does not necessarily indicate the presence of a highly acidic component in the sulfate aerosol. Examination of the extent to which sulfate can be distributed in the environment does give some indication of the possible spatial extent of acid sulfate in the worst possible case (i.e., little neutralization). The most extensive data base on the regional nature of sulfate in the Eastern U.S. was acquired during the SURE Project. Figure 2-12 shows the monthly average SO_4^{-2} concentrations and the change over the course of a year of the magnitude and the spatial extent of

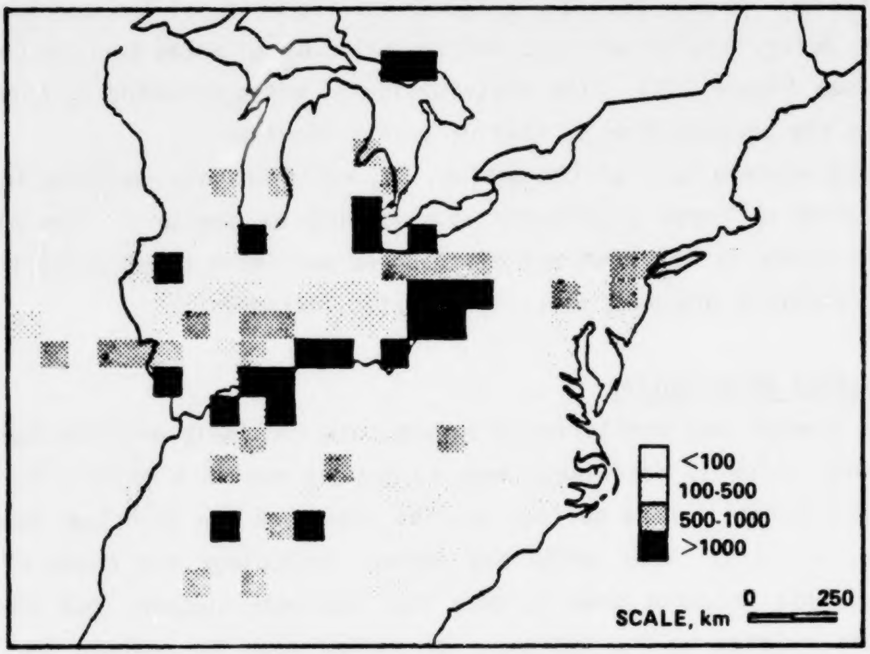
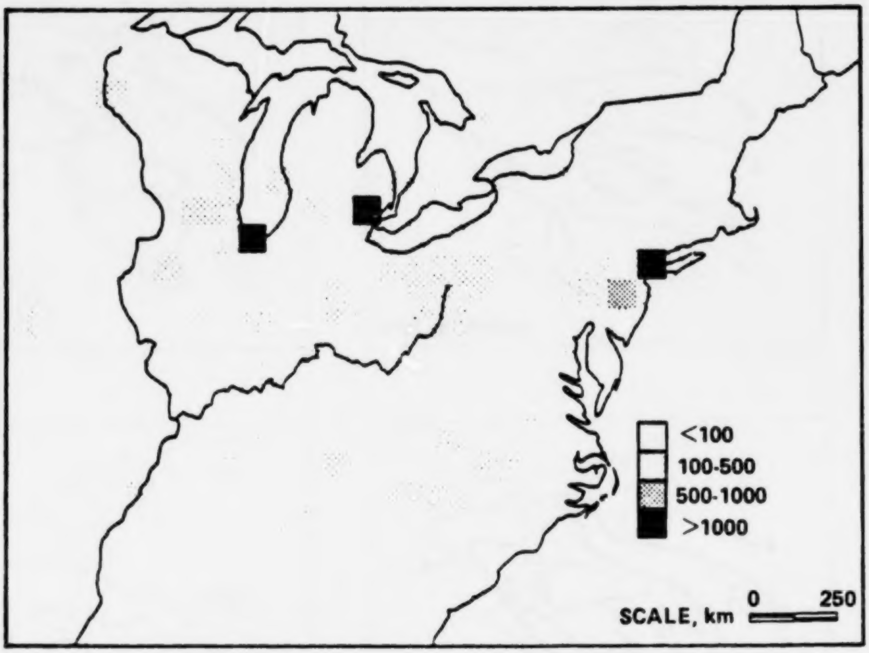

<100
100-500
500-1000
>1000
0
250
SCALE, km

Figure 2-10. Distribution of SO_2 emissions in the SURE area for summer (metric tons/day). Emissions are based on data representative of 1977.

Source: Mueller and Hidy (1983).



<100
100-500
500-1000
>1000
0
250
SCALE, km

Figure 2-11. Distribution of NO_x emissions in the SURE area for summer (metric tons/day). Emissions are based on data representative of 1977.

Source: Mueller and Hidy (1983).

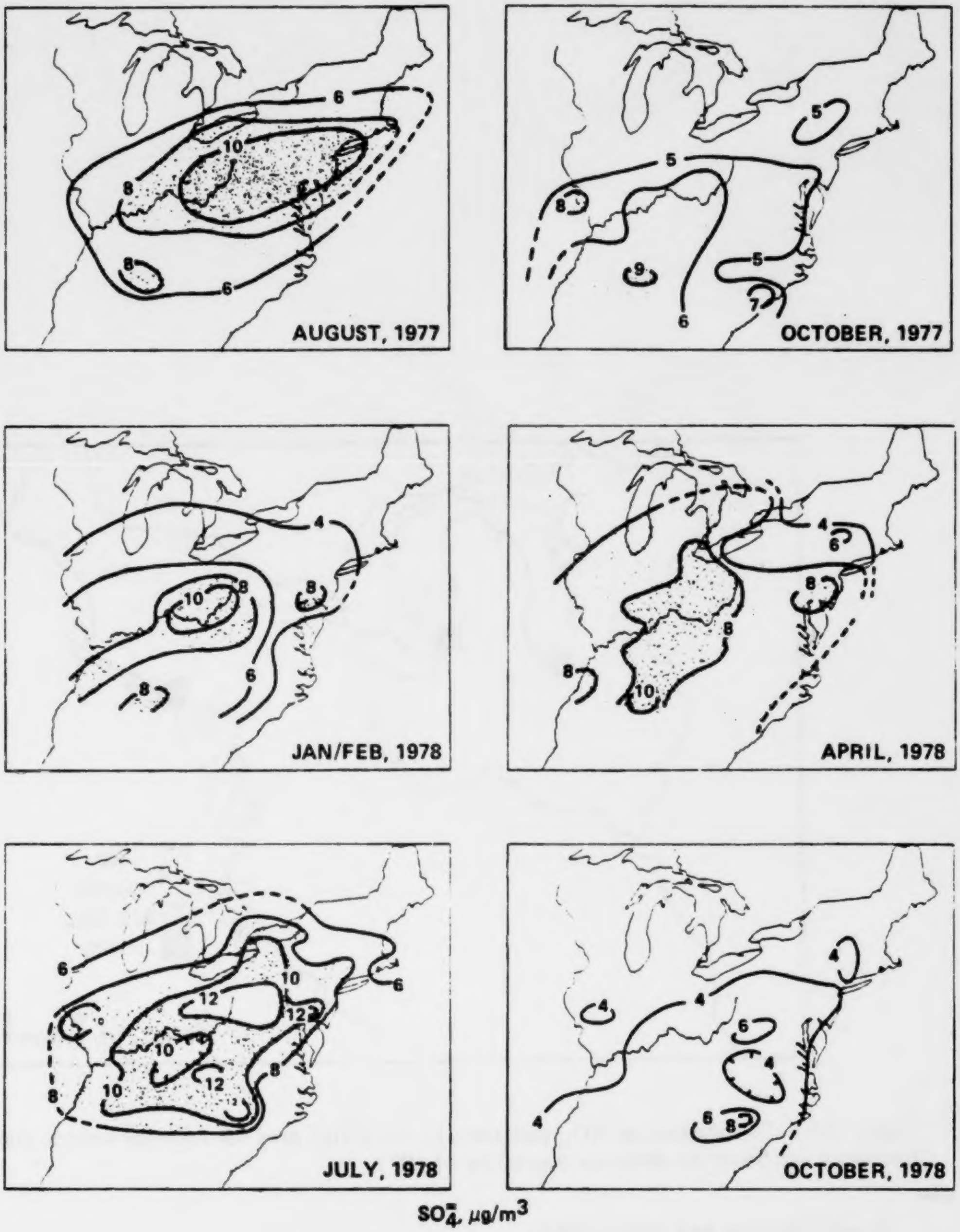

AUGUST, 1977
OCTOBER, 1977
JAN/FEB, 1978
APRIL, 1978
JULY, 1978
OCTOBER, 1978
$SO_4^=$, µg/m^3

Figure 2-12. Monthly average distribution of 24-hour HIVOL particulate sulfate concentrations in the eastern United States.

Source: Mueller and Hidy (1983).

such concentrations. The data also indicate that a significant portion of the Eastern U.S. experiences average sulfate levels above 8 μg/m^3.

The peak sulfate values recorded in SURE were in excess of 25 μg/m^3 during the summer with lower values during the winter. The higher concentrations shifted to the southeast during the winter. In the Airborne Toxic Elements and Organic Substances (ATEOS) study conducted at four sites in New Jersey during 1981-1983 mean values of approximately 10 μg/m^3 were observed at each site (Lioy and Daisey, 1986). Sulfate excursions were above 30 μg/m^3 during the summer, and above 20 μg/m^3 on a few occasions during the winter. The Particulate Matter - Sulfur Oxides Criteria document (U.S. Environmental Protection Agency, 1982a) states that on the West Coast the area around Los Angeles has annual average sulfate values above 8 μg/m^3. Hidy (1986) published data indicating a peak concentration of SO_4^{-2} of 24.3 μg/m^3 in Los Angeles in 1977.

The regional relationship between SO_4^{-2} and SO_2 present at the SURE monitoring sites was examined using the ratio of sulfate sulfur to total airborne sulfur (SO_4^{-2} and SO_2). The results for each season are shown in Figure 2-13. These findings indicate that the seasonal average of the SO_4^{-2}/Total S ratio for summer was much higher than ratios for the winter. During the winter, the ratios were substantially lower in the northern part of the SURE study area than in the southern and the coastal sections. These differences were consistent with the expectation of both greater rates of SO_2 conversion to SO_4^{-2} and greater losses by dry deposition of SO_2 during the summer months and in the south during winter months. During any of the seasons, the maximum ratios usually occurred within 80 to 200 km of the major source areas. These findings show that most of the conversion to SO_4^{-2} or SO_2 dry deposition were associated with mesoscale meteorology even during regional sulfate events. This latter point suggests that concentrations of the acidic portion of the SO_4^{-2} aerosol may be enhanced in areas downwind of urban or stationary source plumes. The work of Gillani (see Section 2.2) was strongly suggestive of the formation of sulfur aerosol in a variety of plume conditions.

2.5 HISTORIC ACID LEVELS

2.5.1 London Sulfuric Acid Data

A relationship between air pollution and mortality/morbidity was recognized in England, especially after the severe London fog episode of

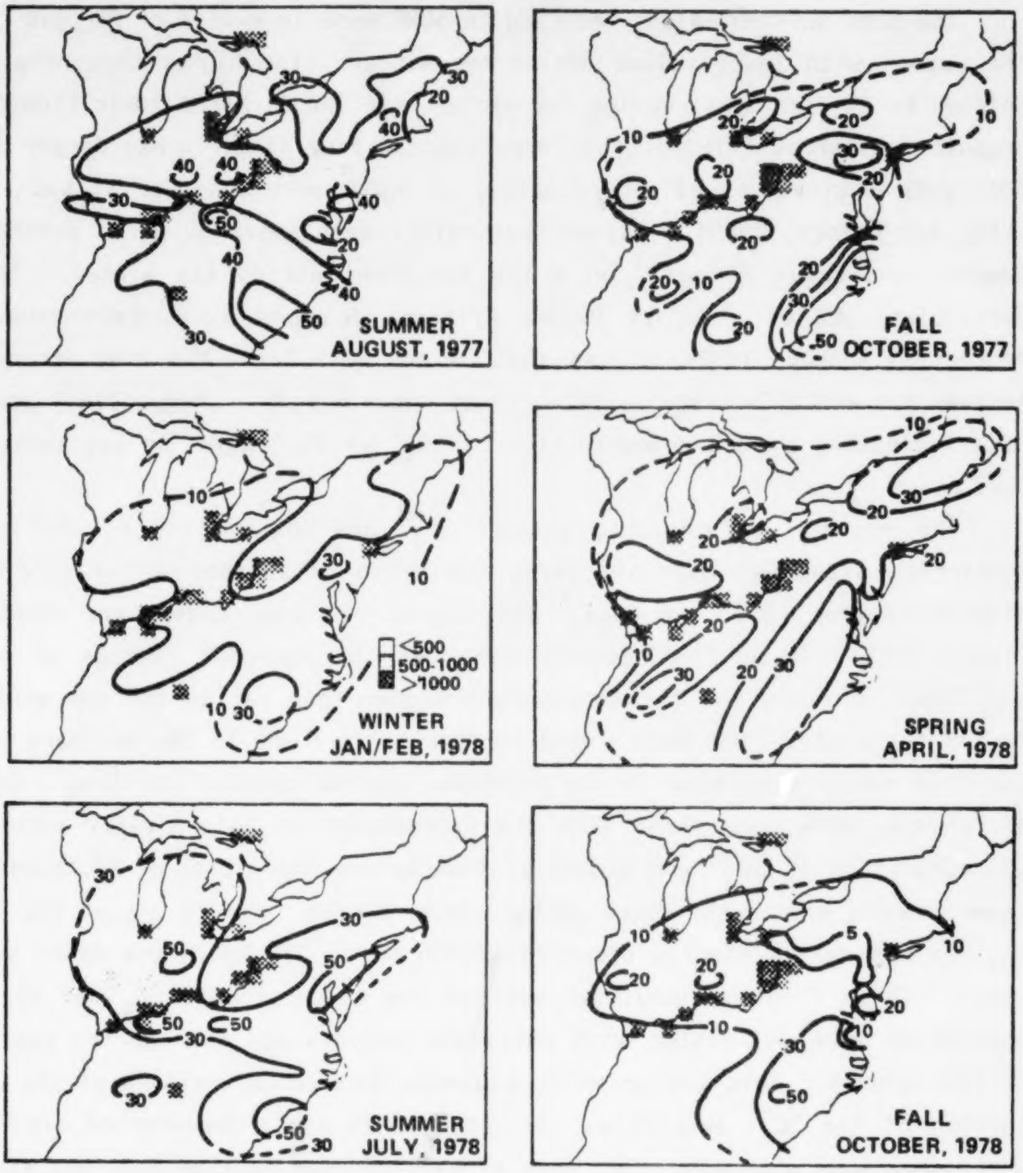

SUMMER
AUGUST, 1977
FALL
OCTOBER, 1977
WINTER
JAN/FEB, 1978
<500
500-1000
>1000
SPRING
APRIL, 1978
SUMMER
JULY, 1978
FALL
OCTOBER, 1978

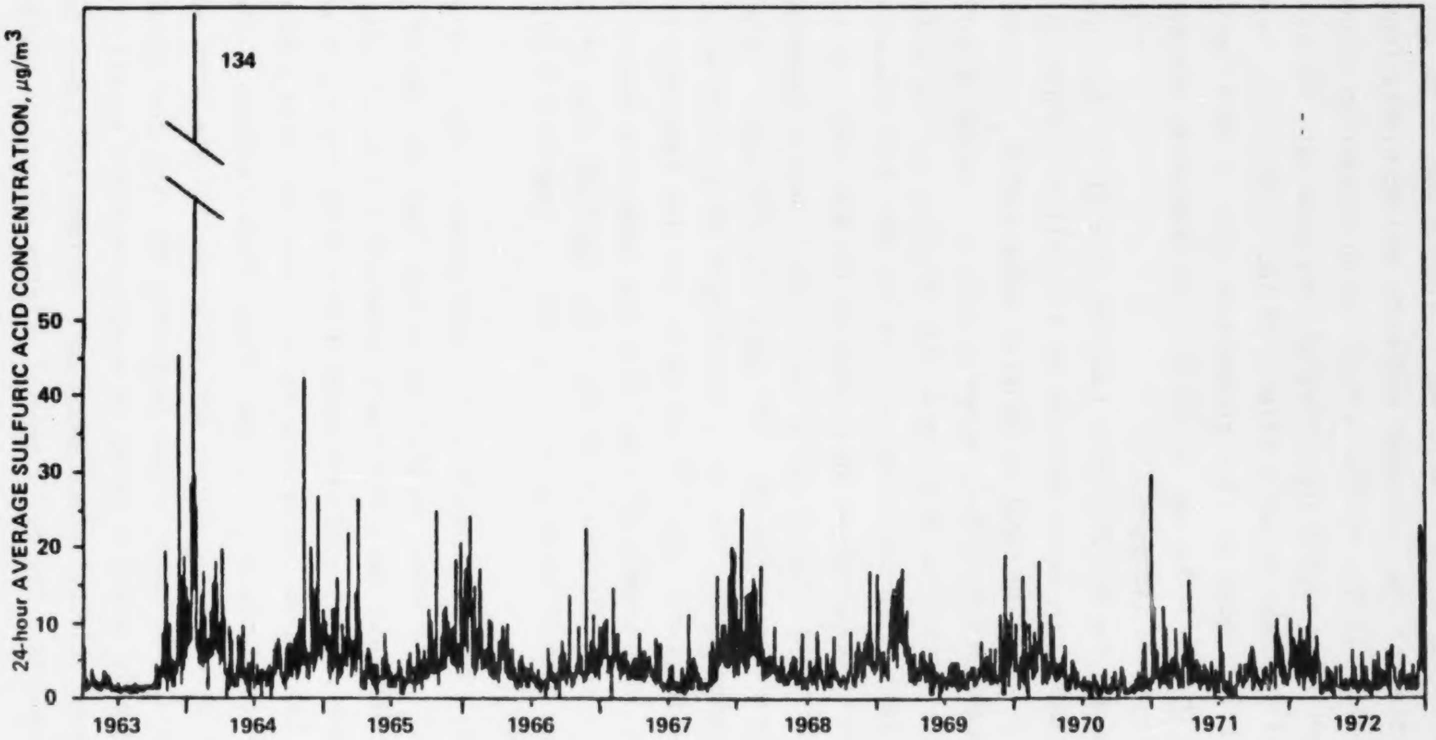
Figure 2-13. Geographical distribution of the ratio of sulfate sulfur to total airborne sulfur for different seasonal periods (in percent).

Source: Mueller and Hidy (1983).

December 5-8, 1952. Although sulfuric acid was considered one of the pollutants possibly responsible for the increased mortality and morbidity (United Kingdom Ministry of Health, 1954), routine air pollution monitoring conducted by local authorities and other regulatory bodies did not have data for sulfuric acid. Some inferential information was available to implicate acids, however, from samples collected in London on five consecutive days in 1934 (Mader et al., 1950). Seven to 9.5 h average sulfuric acid concentrations were measured that ranged from 0 to 148 $\mu g/m^3$.

Following the episode, the Air Pollution Research Unit at St. Bartholomew's Hospital started an elaborate research program on air pollution (Commins and Waller, 1967). Their daily measurement of British Smoke and SO_2 started in January 1954. The concentrations of some other pollutants, including sulfuric acid calculated from net aerosol acidity, were also measured during episodes and, later, on a daily basis. In their ten years of air pollution measurements (1954-1964), sulfuric acid measurements were reported for episodes starting in the winter of 1957/1958. The highest daily and highest hourly apparent sulfuric acid concentrations recorded were 347 $\mu g/m^3$ and 678 $\mu g/m^3$, respectively, on days in December 1962. The daily measurement of sulfuric acid was begun during April 1964 (Figure 2-14). It was noted that the sampling site at the Medical College was in a commercial area, that the smoke came mainly from domestic heating sources some distance from the site, and that much of the sulfur dioxide came from central heating installations in commercial buildings (Commins and Waller, 1967).

The analytical method for the aerosol acidity measurements was reported in detail by Commins (1963). The total particulate matter from the sampled air was collected by filtration, and the filters were immersed in a known excess of 0.01 N sodium tetraborate and titrated back to pH 7 with 0.01 N sulfuric acid. This procedure allowed the sodium tetraborate to neutralize the acid before it was neutralized by the insoluble base on the filter (interference). The interferences by acidic gases, basic gases, and other particulate acids were reported to be negligible. Although it was suggested that the predominant acid in the air was sulfuric acid, it would be more appropriate to call the measured index 'net strong acidity' since ammonium bisulfate could have been present in significant amounts. The daily aerosol acidity values are plotted



ANNUAL

AVERAGE	6.8	5.1	4.6	4.1	4.5	4.3	3.0	3.2	3.2
STD. DEV.	9.6	3.4	3.2	2.9	2.9	3.0	2.5	2.7	2.7
MAXIMUM	134.1	26.3	24.3	20.2	25.3	19.0	18.2	29.7	22.9

WINTER MONTHS (NOV. 1 - FEB 29)	63-64	64-65	65-66	66-67	67-68	68-69	69-70	70-71	71-72
AVERAGE	10.4	7.3	7.5	5.2	7.6	6.0	4.8	3.3	4.5
STD. DEV.	15.5	5.0	4.1	2.7	3.9	3.2	2.9	3.7	2.4
MAXIMUM	134.1	42.2	24.3	22.5	25.3	17.0	19.0	29.7	13.7

Figure 2-14. Historical London daily aerosol acidity data. (Total H^+ as sulfuric acid)

Source: Ito and Thurston (1987).

in Figure 2-14 and averages, standard deviations, and maximums for years and winter months (November 1 through February 29) are noted. Also, 9 a.m. hourly total aerosol acidity data are available from 1965, though with no weekend data and less completeness. It can be seen in Figure 2-14 that H^+ concentration was usually highest during the winter, probably due to increased heating fuel usage and adverse meteorological conditions. A gradual decrease in acid concentration due to a Smoke Control Order can also be seen.

2.5.2 Los Angeles Data

In 1949 a study was conducted in Los Angeles, California to determine the amount of free sulfuric acid in the atmosphere during periods of intense fog and on clear days (Mader et al., 1950). The results for four separate 1-hour sampling periods indicated a range in concentration from 0 to 157 $\mu g/m^3$. There were two days with levels above 150 $\mu g/m^3$ and each occurred on a day with high relative humidity.

2.6 METHODOLOGY FOR STRONG ACID MEASUREMENT

Atmospheric strong acids consist principally of sulfuric and nitric acids derived from the oxidation of sulfur dioxide and nitrogen oxides emitted from stationary and for NO_x mobile combustion sources (National Research Council, 1983). Some evidence suggests that hydrochloric acid may also be present in the atmosphere (Rahn et al., 1979) derived from primary, coal-fired utility emissions or evolved due to interactions between sea salt and acidic sulfate aerosols. These species are neutralized principally by atmospheric gaseous ammonia (the latter mostly originated from surface biogenic and anthropogenic sources) and soil-derived particulate matter to produce the observed composition of sulfate and nitrate aerosols and the levels of nitric acid found in the atmosphere (Brosset et al., 1975; National Research Council, 1977).

Research efforts in progress on acid species are dependent on the development and application in the last 10 to 20 years of techniques for rapid, accurate, microscale determination of total strong acid and of individual acidic species in atmospheric aerosol and gaseous samples. This section details these technical developments, concentrating largely on acidic aerosols;

although, a brief section is provided on nitric acid measurements. These techniques consist mostly of filter-based schemes but with some continuous and/or real-time approaches. Sampling/analysis protocols are recommended that minimize analytical complications.

2.6.1 Methodologies for Strong Acids and Sulfuric Acids

Descriptions of methodologies for strong acids in aerosols are arranged according to the measurement principle: filter collection and post-collection extraction, derivatization and analysis, or real-time, in situ analysis--and further segregated according to whether total aerosol strong acid content is measured or individual species are determined.

2.6.1.1 Sulfuric Acid

2.6.1.1.1 Filter collection. Thermal volatilization schemes were popular for several years for speciation of acidic sulfate compounds in aerosols. Filter samples were heated and H_2SO_4 collected by microdiffusion (Scaringelli and Rehme, 1969; DuBois et al., 1969) or determined directly by flame photometry after volatilization from Teflon filters (Richards and Mudgett, 1974; Richards et al., 1978). In one method, H_2SO_4 was distinguished from other volatile sulfates (e.g., NH_4HSO_4 and $(NH_4)_2SO_4$), and nonvolatile sulfates (e.g., Na_2SO_4) by heating in sequence at two different temperatures (Leahy et al., 1975). In another approach, 2-perimidinylammonium sulfate was formed from acid sulfates and thermally decomposed to SO_2 for West-Gaeke analysis (Maddalone et al., 1974).

These methodologies were stimulating attempts to analyze acidic sulfate aerosols for individual species. However, due to serious recovery problems (Leahy et al., 1975) and limited success in distinguishing the two major aerosol species (NH_4HSO_4 and $(NH_4)_2SO_4$) from each other (Thomas et al., 1976), the methods have fallen into disfavor with three exceptions. One technique uses a temperature-cycled diffusion denuder tube in connection with a real-time flame photometric detector (FPD) to determine H_2SO_4 in ambient aerosols (Tanner et al., 1980; Allen et al., 1984). A related technique uses a series of denuder tubes at varying temperatures to collect nitric acid, sulfuric acid and bisulfate constituents separately for integrated analysis with several-hour time resolution (Slanina et al., 1981). Recently the heated denuder system has been mated with a flame photometric detector to produce a computed-controlled system for H_2SO_4, ammonium acid sulfates and nonvolatile sulfate with time resolution of 5 min to 1 h depending on requisite sensitivity (Slanina et al., 1985). A photoionization detector has also been used for the determination of H_2SO_4 after preconcentration in a denuder and gas chromatographic separation (Lindqvist, 1985). A related technique determines nitric acid by denuder tube collection with subsequent decomposition to NO_x and determination by ozone-chemiluminescence (Klockow et al., 1982).

2.6.1.1.2 Extraction with pH measurement or H^+ titration. Filter-collected samples may be analyzed for net strong acid content by extraction into water or dilute mineral acid. The extracted free acid content may be determined by simple measurement of pH and, in the absence of weak acids, equated to the amount of strong acid originally present in the sample. However, this determination can be in error because of the potential presence of buffering agents such as weak carboxylic acids or hydrated forms of heavy metal ions; e.g., Fe(III) and Al(III) (Commins, 1963; Junge and Scheich, 1971).

Titration procedures for strong acid employing a logarithmic display of data points (Gran titration) were originated by Junge and Scheich (1971) perfected by Brosset and co-workers (Brosset and Ferm, 1978; Askne and Brosset, 1972), and used widely by other groups (Stevens et al., 1978; and Liberti et al., 1972). Coulometric generation of strong base for Gran titrations has been used by several groups (Liberti et al., 1972; Krupa et al., 1976; Tanner et al., 1977). Dissolution of filter samples in 0.1 mM mineral acid followed by Gran titration with correction for the blank (Tanner et al., 1977) allows for titration of 1 μmole levels of strong acid with precision and accuracy better than ±10 percent (Stevens et al., 1978; Phillips et al., 1984).

The presence of partially dissociated weak acids, i.e., with pk_as in the range of the aqueous extract of aerosols can lead to overestimates of strong acid contents (Lee and Brosset, 1978). The extent of this error source was discussed by Keene and Galloway (1985) for precipitation samples in which weak acids were preserved from microbial decomposition. Standard protocols for aerosol collection and strong acid determination do not include preservation, which explains the absence of significant qualities of weak acids in atmospheric aerosol samples (Ferek et al., 1983) and validates the use of Gran titration approaches with continuous addition of titrant for strong acid quantitation in those samples.

2.6.1.1.3 Specific extraction of atmospheric acids. Most of the effort in specific extraction of atmospheric acids has related to aerosol H_2SO_4 analysis.

Benzaldehyde has been shown to be specific for H_2SO_4 in dried acidic aerosol sulfate/nitrate samples with analysis for sulfate in aqueous back-extracts (Leahy et al., 1975). Isopropanol (Barton and McAdie, 1971) quantitatively extracts H_2SO_4 from quartz filter media but also removes ammonium bisulfate phases (Leahy et al., 1975). The behavior of isopropanol as an extractant is not well characterized for mixed nitrate/sulfate aerosols. In addition, difficulties have been reported with quantitative removal and selectivity of extraction using the benzaldehyde extraction technique (Appel et al., 1980; Eatough et al., 1978). Since free H_2SO_4 is not a common constituent of ambient aerosols, use of specific extractant methodologies has decreased in recent years in favor of generic strong acid determinations.

2.6.1.1.4 Specific extraction with derivatization. A method has been proposed for derivatization of collected H_2SO_4 by dry diethylamine followed by reaction with CS_2 and cupric ion to form a colored complex for spectrophotometric determination (Huygen, 1975). This method suffers from a large ammonium bisulfate interference. Likewise an approach in which filter-collected H_2SO_4 is converted to dimethylsulfate by reaction with diazomethane, with subsequent analysis by gas chromatography-flame photometric detection, does not specifically determine H_2SO_4 in the presence of ammonium bisulfate and sulfate salts (Penzhorn and Filby, 1976; Tanner and Fajer, 1981). A related method, by which H_2SO_4 and other aerosol strong acids are converted to ^{14}C-labelled bis(diethylammonium) sulfate and analogs, is useful for determination of low levels of strong acid in aerosols (Dzubay et al., 1979), but is also not specific for H_2SO_4.

2.6.1.1.5 Continuous and/or real-time analysis. Sulfuric acid may be determined using a continuous flame photometric detector (FPD) although such measurement is not real-time and represents an average concentration over a few-minute period (Tanner et al., 1980; Allen et al., 1984; Slanina et al., 1985). The technique uses a diffusion denuder tube for SO_2 removal attached to an FPD, identical to the instrumentation for a continuous aerosol sulfur analyzer as described by a few groups (Huntzicker et al., 1978; Cobourn et al., 1978; Camp et al., 1982; Morandi et al., 1983). However, the temperature of the denuder tube or a zone just upstream therefrom is cycled between room temperature and about 120°C. At ambient temperatures sulfuric acid remains in the aerosol phase, but at 120°C, it is volatilized and removed in the denuder tube. The difference in response between ambient temperatures and 120° represents ambient

H_2SO_4 levels. The minimum cycle time and hence time resolution for the technique is about 6-8 min. Sensitivity-enhanced FPD measurements using SF_6-doped H_2 fuel gas are required for ambient measurements (D'Ottavio et al., 1981).

Acidic sulfates including sulfuric acid may also be differentiated using humidograph techniques (Charlson et al., 1974) and recently developed thermidograph variations (Larson et al., 1982; Rood et al., 1985). This latter technique involves heating the aerosol-containing air stream progressively from 20°C to 380°C in 5 min cycles, rapidly cooling it to the dry bulb temperature and measuring the light scattering at 65 to 70 percent RH with a nephelometer. By comparing the results with the thermidograms of test aerosols, the fractional acidity can be measured and approximate level of H_2SO_4 determined.

The fractional acidity can also be determined using an impactor: attenuated total reflectance (ATR), Fourier-transform infrared (FTIR), spectroscopic technique (Cunningham and Johnson, 1976). Impactor samples are pressed into a KBr matrix and the IR spectrum used to determine the relative acid and qualitatively identify aerosols with molar H^+/SO_4^{-2} ratios >1, the condition for the presence of H_2SO_4 in the aerosol samples.

2.6.1.2 Nitric Acid

2.6.1.2.1 Nitric acid sampling techniques. A summary of techniques presently employed in nitric acid sampling is found in Table 2-6 (Stevens, 1986). All are filter techniques that can include multiple hour or multiple day samples. Research grade instrumental HNO_3 samplers are available that use chemiluminescence, tunable diode laser infrared spectroscopy, or Fourier transform infrared spectroscopy as the operating principle.

Unlike the situation for acid sulfates, nitric acid technique intercomparisons were made in the Claremont, CA intercomparison study (Spicer et al., 1982). This particular intercomparison did not include the annular denuder system described in Table 2-6. A second intercomparison involving eighteen instruments was conducted at Pomona College, CA during September, 1985 (Hering, 1986). The results from this particular experiment reported nitric acid values that varied by a factor of two or more on all sampling days with the differences increasing with loading. It appears that the technology for nitric acid determinations still requires examination, including the development of a reference standard.

TABLE 2-6. DESCRIPTION OF SAMPLING SYSTEMS AND INSTRUMENTS THAT MEASURE CHEMICAL SPECIES THAT CONTRIBUTE TO ACIDIC DRY DEPOSITION

Method	Sampling rate (LPM)	Sampling period	Denuder type and coating	Filter type	Species measured
DDM Cyclone, Denuder Filter Pack System	Denuder, 1 Filter Pack, 2	7 day	300 mm x 4 mm tube coated with $MgCO_3$	Nylon (25 mm) Teflon (47 mm) TEA treated Whatman	Fine particle nitrate, HNO_3, SO_4^{-2}, SO_2, NO_2
AIHL Filter Pack	20	4-24 hrs	N/A	Teflon (47 mm followed by NaCL treated W41)	Fine particle nitrate, HNO_3, SO_4^{-2}, SO_2, NO_2
Modified Canadian Filter Pack	14 1.5	1 day 7 day	N/A	(1) Teflon (2) Nylon (3) W41 Na_2CO_3 treated	SO_4, Total Nitrate, SO_2
Cyclone-Denuder Filter Pack Concentration Monitor	15	>12 hr	320 mm x 10 mm Nylon lined tube	Teflon, Nylon TEA treated W41	HNO_3, NH_3, H^+, SO_4^{-2}, SO_2, NO_2, Nitrate
Cyclone-Annular Denuders-Filter Pack in Series	1 4 15	7 day 24 hr 12-24 hr	Annular design[1] Na_2CO_3 (SO_2, HNO_3, HNO_2) Citric Acid (NH_3)	Teflon, Nylon TEA treated W41	HNO_3, HNO_2, SO_2, HCl, NH_3, SO_4^{-2}, H^+, Nitrate, NO_2 and fine particle mass
NOAH Filter Pack	3	7	N/A	Teflon Nylon W41, Na_2CO_3	SO_4^{-2}, Total Nitrate, SO_2
Tungstic Acid Diffusion Tube	1	30 min	200 mm x 3 mm WO_2		HNO_3 and NH_3
Chemiluminescent Methods	1	1 min	N/A	N/A	O_3, SO_2, NO_x

[1] Annular design is 20 times more efficient in removing gases than tubular designs of equivalent length and Reynolds number operation.

[2] Sensitivity of the methods listed in this table which directly derive the analysis value from a filter or denuder is approximately 0.1 $\mu g/m^3$ assuming at least $2m^3$ of air is sampled.

Source: Stevens (1986).

2.6.2 Sampling Anomalies

Sampling anomalies have plagued the measurement technologies for atmospheric strong acids present in the gas phase or as aerosols, justifying a separate section on the nature of these artifact problems and suggested sampling techniques to minimize their effects. These sampling problems generally fall into two classes: (1) reversible or irreversible sorption losses onto filter materials in integrative methodologies or onto sampling lines in continuous and real-time techniques; (2) equilibrium-driven loss or gain of species due to non-steady-state conditions in the sampled atmosphere over the time period of the measurement. Both of these phenomena affect sampling/analysis techniques for strong acids in the atmosphere and are discussed below.

2.6.2.1 Sorption Losses. Studies of sorption losses on filters have centered on three major areas related to measurement of strong acid content in atmospheric samples. One area is the loss of strong acid in aerosol particles by reaction with basic sites in the filter matrix used to collect the particles (Appel et al., 1979). Filter matrices used for high-volume sampling include glass fiber or cellulose. These media, particularly glass fiber filters of all types, are unsuitable for collection of acidic aerosol particles for subsequent extraction and titrimetry (Tanner et al., 1977; Appel et al., 1979; Coutant, 1977). This is true even if the glass fiber filters are pretreated with acid as well as fired to high temperature, since subsequent rinsing exposes additional free basic sites in the glass, resulting in neutralization of the sample (Tanner et al., 1977). High-purity quartz filters can be pretreated to remove basic sites for high-volume sampling, hence, treated quartz and Teflon filter media have generally replaced glass fiber or cellulose filters for sampling of acid aerosols by high-volume and low-volume techniques, respectively.

The filter treatments described above also eliminate a positive source of error in sulfate measurements - the artifact sulfate formed by base-catalyzed oxidation of SO_2 (sorbed on the filter surface) to form sulfuric acid (Coutant, 1977; Pierson et al., 1976; Pierson et al., 1980a). The acid so formed is neutralized on the filter surface, but the residual sulfate remains and is measured using standard extraction/analysis techniques.

A third problem is the loss of strong acid contents by topochemical reactions between co-collected basic and acidic particles on the filter surface. This most frequently occurs as the result of coarse (>2.5 μm), alkaline, soil derived particles interacting with fine (<2.5 μm), acidic sulfate particles (Camp, 1980; Spicer et al., 1978; Tanner et al., 1979). This problem can be eliminated by sampling with a dichotomous sampler, by high-volume sampling with a cyclone to remove coarse particles, or by sampling for shorter time durations. In connection with the latter solution, sampling in most ambient environments for ≤3 h results in low enough surface coverage to prevent topochemical reactions, but this procedure does not prevent neutralization during subsequent extraction procedures.

2.6.2.2 Equilibria-Driven Losses. Equilibria involving gas- and particulate-phase species may lead to artifactual errors in sampling strong acids as well as other species in the atmosphere under both steady-state and non-steady-state conditions. Thermodynamic considerations suggest that aerosol sulfuric acid/ sulfate mixtures should be in dynamic equilibrium with atmospheric ammonia (Lee and Brosset, 1979). Indeed, as noted initially, ammonia is believed to be the principal neutralizing agent for sulfuric acid formed by heterogenous or homogenous oxidation of SO_2. However, the equilibrium level of NH_3 for even slightly acid sulfate is much below the usually observed ambient NH_3 levels. This suggests that a non-steady-state, mixing-limited situation normally exist (Appel et al., 1979) or, alternatively, that mixed nitrate/sulfate salts are usually present with their concomitantly much greater equilibrium NH_3 concentrations.

2.6.3 Recommended Protocols

2.6.3.1 Strong Acid Aerosols. The discussion above indicates that a recommended method for analysis of strong acid in aerosols is collection on inert filter media, ultrasonic extraction into weak acid (ca. 0.1 mM) and titration with base using a Gran plot to determine the equivalency point. In some cases a pH measurement of the extract can be sufficient. For sampling periods longer than a few hours (depending on ambient levels), a virtual impactor-based sampler that collects particles on Teflon filter media should be used. With shorter term sampling for which high-volume apparatus is required, acid-treated quartz filters can be used, preferably ones with a cyclone pre-separator for coarse particle removal. Automation of the titration procedure using coulometric generation of hydroxide is a practical necessity when large numbers of samples must be processed. Precision and accuracy approaching ±10 percent is possible with careful flow calibration and for sample sizes exceeding 0.5 μeq (≥25 μg as H_2SO_4) (Phillips et al., 1984).

2.6.3.2 Specific Determination of H_2SO_4. No method is fully satisfactory for determining the low levels of H_2SO_4 occasionally found in ambient aerosols. Two approaches that may be used with reasonable success are the following. Filter pack samples, collected on treated quartz filters that are then thoroughly dried over desiccant, may be extracted into benzaldehyde, the sulfate therein then back-extracted into water and determined by ion chromatography or other soluble sulfate methodologies (Leahy et al., 1975; Tanner et al., 1977). Careful drying of the filter is required, as noted above, to prevent significant interference from ammonium bisulfate (usually present in excess of H_2SO_4); in addition an impurity, benzoic acid, in the benzaldehyde may be present in amounts sufficient to interfere with ion chromatography or other sulfate determinations. Sulfuric acid may also be determined by flame photometry using a temperature-cycled diffusion denuder tube (Tanner et al., 1980; Allen et al., 1984). Time resolution is limited by the minimum temperature cycle time of the denuder (5 to 10 min) and is quite adequate. However, the limit of detection, only about 1 $\mu g/m^3$ H_2SO_4 even with sensitivity enhancement through use of SF_6 -doped H_2 unless denuder concentration is used (Slanina et al., 1985), is not adequate for many ambient applications. Direct denuder tube collection of H_2SO_4 in heated denuders is a viable alternative. The time resolution is several hours if extraction and wet chemical analysis is used due to the necessarily slow flow rate through denuder tubes.

2.6.4 Applications

The results from studies that have been conducted over about the past twelve years on strong acid sulfate and sulfuric acid are reported in next section. These studies have used a variety of quasi-continuous and integrated sampling methods. Only the most recent studies have systematically used approaches similar to those recommended in Section 2.6.3. The development of the recommended techniques represent the advancements made by individual investigators. No organized program exists to develop recommended techniques. No program is currently in place that evaluates the relative uncertainties of the methods employed in the individual studies. Major efforts to examine the national exposure to acidic aerosol will require the development of a quality assurance program and a program to examine which pre-collection devices will be necessary to minimize alteration of the acid concentration actually present in the atmosphere.

2.7 ATMOSPHERIC CONCENTRATION

2.7.1 Atmospheric Acidic Sulfate Studies from 1974 to 1986

Results of field investigations of the surface concentration of acidic sulfate species in the United States and Canada since 1974 are shown in Table 2-7. A variety of sampling strategies and analytical methods were used, and the individual sampling times ranged from 1 to 24 hours.

Most of the studies reported in Table 2-7 were conducted during the summer. This is the season when large scale regional ozone and SO_4^{-2} smog episodes, which last at least three days, can or have occurred in the eastern U.S. and Canada (Wolff and Lioy, 1980; Wolff et al., 1981). In addition, photochemical smog episodes frequently occur in Los Angeles, CA (Hidy et al., 1980) and Houston, TX (Beck and Tannahill, 1978). The magnitude of the wintertime levels of acid sulfate species were derived from a more limited data base, which is also described in Table 2-7. Spengler et al. (1988) reports daily concentrations of H^+ ion for a minimum of nine consecutive months in four United States cities that show a seasonal pattern with lower concentrations in the winter and higher levels in the summer months.

The ranges of SO_4^{-2}, H^+ (as H_2SO_4) and/or H_2SO_4 concentrations recorded in these studies are shown in Table 2-8. It is apparent that a wide range of SO_4^{-2} levels were encountered in acid aerosol studies with the peak concentration being 75 $\mu g/m^3$ for an 8 h period in North America (Waldman et al., 1987). At other times, each study recorded SO_4^{-2} decreases to as low as 0-2 $\mu g/m^3$. The peak H_2SO_4 value, measured with a flame photometric detector (FPD), was 41 $\mu g/m^3$ (1 h average) in 1984 at a site in St. Louis, MO (Ferris and Spengler, 1985).

A H^+ concentration (as equivalent H_2SO_4) of 39 $\mu g/m^3$ was observed in 1975 just northeast of St. Louis in Glasgow, IL (Tanner and Marlow, 1977). The striking features of the Glasgow data were: (1) the H^+ was measured in the fine particle size range; (2) the measurements were 12 hour duration samples, and (3) the visibility maps indicate the development of an urban plume from St. Louis. A comparison of the $\{H^+\}/(\{H^+\} + \{NH_4^+\})$ ratio on July 29, 1975 indicated that the aerosol in Glasgow, IL contained both NH_4HSO_4 and H_2SO_4.

A number of other studies also indicated the presence of both species (Tanner and Marlow, 1977; Morandi et al., 1983; Huntzicker et al., 1984; Lioy and Lippmann, 1986). Pierson et al. (1987) completed a study at both

TABLE 2-7. A SUMMARY OF REPRESENTATIVE NORTH AMERICAN ATMOSPHERIC STUDIES DURING WHICH ACID SULFATE OR TOTAL ACIDITY WAS MEASURED BY ONE OR MORE TECHNIQUES

Location	Acid Species Measured	Dates	Method for Acid Determinations	Reference
St. Louis, MO	Inferred Acid Sulfates	August-October 1973	Humidographs/ Light Scattering	Charlson et al. (1974)
Glasgow, IL	Hydrogen ion	July 20-30, 1975	Titration	Tanner and Marlow (1977)
Research Triangle Park, NC	Hydrogen ion	July 27-31, 1977	Titration	Stevens et al. (1978)
St. Louis, MO	H_2SO_4	July 1977-June 1978	Flame Photometry Detection	Cobourn et al. (1979, 1982)
High Point, NJ	Hydrogen ion	August 1-15, 1977	Titration	Lioy et al. (1980)
New York City	Hydrogen ion	August 1-15, 1977	Titration	Tanner et al. (1981)
Allegheny Mountain, PA	Hydrogen ion	July-August 1977	Titration	Pierson et al. (1980)
Great Smokey Mountains, TN	Hydrogen ion	August 20-26, 1978	Titration	Stevens et al. (1980)
Lennox, CA	H_2SO_4, Hydrogen ion	July 12-19, 1979	Titration (H^+), extraction (H_2SO_4)	Appel et al. (1982)
Shenandoah Valley, VA	Hydrogen ion	July-August 1980	Titration	Stevens (1983)
Houston, TX	Hydrogen ion	August 1980	Titration	Stevens (1983)
Tuxedo, NY	Hydrogen ion, H_2SO_4	August 1980	Titration, FPD-TA	Morandi et al. (1983)
Mendham, NJ	Hydrogen ion	July-August 1982	4 and 8 h Titration	Lioy and Lippmann (1986)

(continued on the following page)

TABLE 2-7. (continued)

Location	Acid Species Measured	Dates	Method for Acid Determinations	Reference
St. Louis, MO	H_2SO_4	August 3-10, 1979	FPD-TA	Huntzicker et al. (1984)
St. Louis, MO	H_2SO_4	November 1983-March 1984	FPD-TA	Ferris et al. (1985)
Los Angeles, CA	Hydrogen ion	August 1983	Titration	
Harriman, TN	H_2SO_4	March-December 1984	FPD-TA	Spengler et al. (1986)
Watertown, MA	H_2SO_4	1984	FPD-TA	Spengler et al. (1986)
Fairview Lake, NJ	Hydrogen ion, H_2SO_4	July-August 1984	FPD-TA	Lioy and Lippmann (1986)
Warren, MI	Hydrogen ion	June 1981-1982	Titration	Cadle (1985)
Whiteface Mountain, NY	Hydrogen ion	January-December 1984	NA	Kelly et al. (1985)
Nova Scotia, Canada	Hydrogen ion	August 18-September 11, 1983	Titration	Smith-Palmer (1986)
		May 23-July 9, 1984	Titration	
Toronto, Canada	Hydrogen ion	June 30-August 10, 1986	pH by addition	Waldman et al. (1987)
Allegheny Mountain and Laurel Mountain, PA	Hydrogen ion	August 1983	Titration	Pierson et al. (1983)

TABLE 2-8. CONCENTRATION RANGES OF SO_4^{-2}, H+ (as H_2SO_4) AND H_2SO_4 (in μg/m³) MEASURED IN VARIOUS LOCATIONS IN NORTH AMERICAN

Study	Sample Duration Hours	Concentration Range μg/m³) SO_4^{-2}	H_2SO_4	Reference
Glasgow, IL 1977	12	7-48	0-39	Tanner and Marlow (1977)
St. Louis, MO				Cobourn (1979)
1977 Summer	1	5-60	0-28	Cobourn and Husar (1982)
1978 Winter	1	3-24	0-12	
Lennox, CA	2-8	1.2-18	0-11	Appel et al. (1982)
Smokey Mountains	12	6.2-17.4	2.8-9.6	Stevens et al. (1980)
High Point, NJ	6	3.0-36.6	2.2-17.8	Lioy et al. (1980)
Brookhaven, NY	3	1.0-23.7	0.3-10.2	Lioy et al. (1980)
RTP, NC	2,4	3.6-19.8	0-9.8	Stevens et al. (1978)
Allegheny Mt, PA	12	1-32.5	0-20	Pierson et al. (1980b)
Shenandoah Valley, VA	12	2-40	0-23	Stevens (1983)
Tuxedo, NY	1-12	1-41	1-8.7	Morandi et al. (1983)
Mendham, NJ	4,20	1-37.3	0-6.3	Lioy and Lippmann (1986)
Houston, TX	12	2-32.4	0-7.6	Stevens (1983)
New York City	6		nm	Lioy et al. (1980)
St. Louis, MO	QC	3-25	0-7	Huntzicker et al. (1984)
St. Louis, MO	QC	<5-43	0-34	Ferris and Spengler (1985)
Los Angeles, CA	12	3-10	0.6-3.2	John et al. (1985)
Harriman, TN	QC	9-47	0-18	Spengler et al. (1986)
Watertown, MA	QC	5-31	0-14	Spengler et al. (1986)
Fairview Lake, NJ	QC,4	13-27	0-12	Lioy and Lippmann (1986)
Warren, MI	24	.4-36.7	.8-8.7	Cadle (1985)

(continued on the following page)

TABLE 2-8. (continued)

Study	Sample Duration Hours	Concentration Range ($\mu g/m^3$) SO_4^{-2}	Concentration Range ($\mu g/m^3$) H_2SO_4	Reference
Whiteface Mt., NY	24	0-58.9	0-14	Kelly et al. (1985)
Nova Scotia	24	0-26	0-9	Smith-Palmer and Wentzell (1986)
Toronto, Canada	8,16	0-75	0-19.4	Waldman et al. (1987)
Allegheny Mt., PA	7,10	1.7-45.4	0.4-30.5	Pierson et al. (1987)
Laurel Mt., PA	7,10	2.2-55.5	0.5-42.0	Pierson et al. (1987)

Allegheny Mountain and Laurel Mountain in 1983 with observed peak H^+ (as apparent H_2SO_4) concentrations of 30.4 and 42.0 $\mu g/m^3$ at the respective sites.

As stated previously, work by Morandi et al., (1983) included an attempt to infer the distribution of acidic species from coincident instrumental FPD measurements of H_2SO_4 and filter analyses for H^+. The results of that study indicated there was no evidence of the presence of any strong acids (pka <2) other than NH_4HSO_4 or H_2SO_4. On the basis of this observation, and using data from the FPD and filter samples, the SO_4^{-2} associated with H_2SO_4 and NH_4HSO_4 was inferred from the molar differences between the H^+ and the simultaneously measured H_2SO_4 by the FPD (i.e., using equivalent average time periods for the latter data). The results of the analysis showed:

1. The species H_2SO_4, NH_4HSO_4 and $(NH_4)_2SO_4$ can occur simultaneously in a present-day polluted atmosphere.
2. On occasion, SO_4^{-2} will be associated only with H_2SO_4 and NH_4HSO_4.
3. During a period of sustained sulfate concentrations (2 to 3 days) the sulfates change in composition from acid to basic species, (Table 2-5).

The latter observation was made during a large scale regional episode that affected the northeastern U.S. at the end of August 1980.

The 1984 Fairview Lake, N.J. study reported by Lioy et al. (1987) was conducted in a manner similar to Morandi et al. (1983). The species distribution and concentration again showed that the occurrence of H_2SO_4 is quite variable and is usually limited in extent, while NH_4HSO_4 was found over a series of days. The approximate 1 h peak of H_2SO_4 was 12 $\mu g/m^3$.

The 1977-1978 St. Louis, MO study by Cobourn and Husar (1982) showed that levels of H_2SO_4 in excess of 1 to 2 $\mu g/m^3$ occurred sporadically, but most of the time the occurrence of H_2SO_4 was rare. From July 15-18, 1977 St. Louis was influenced by a highly stagnant southerly maritime tropical air mass. The observed 1 h H_2SO_4 was about 6 $\mu g/m^3$ for much of July 17 and 18. In two 1 h intervals, the levels exceeded 20 $\mu g/m^3$. In 1979, a short study (8 days) by Huntzicker et al. (1984) also examined summertime H_2SO_4 in St. Louis. The period of increased acid occurred within a single day, and in this case was determined to be associated with a local power plant, approximately 17 km away.

Winter measurements during the Cobourn and Husar (1982) study were made in 1978. During the period, H_2SO_4 was measured consistently in February and March, but at lower peak levels than observed during the summertime.

For each of the other summertime studies, peaks of H_2SO_4 and/or H^+ were observed sporadically, and based upon the meteorological data, were associated with the presence of a slow moving hazy summertime high pressure system. A major acid sulfate event occurred over the period from August 1 through August 12, 1977 (Lioy et al., 1980). The daily variation of the six hour particulate sulfate, hydrogen ion samples, and the daily maximum ozone concentrations are shown in Figure 2-15. In the multi-site analyses of this period the results of Lioy et al. (1980) for High Point, N.J. and Brookhaven, Long Island, N.Y. showed peak excursions of H^+ at High Point and Brookhaven (separated by 160 km) with the passage of SO_4^{-2}-laden air masses throughout the northeastern U.S. On one day, August 4, 1977, both High Point and Brookhaven were affected by air parcels that had passed over different geographical areas, and only the High Point site recorded high H^+ and SO_4^{-2}.

New York City data for the same period were reported by Tanner et al. (1981). They did not record any acidity during August 4 or on any other of the fifteen sampling days. This suggested that after passing High Point, N.J., the flux of NH_3 emanating from the metropolitan area neutralized the acid laden air parcels. The values of H^+ measured at Brookhaven, L.I., N.Y., were consistently lower than the values measured at High Point, suggesting partial

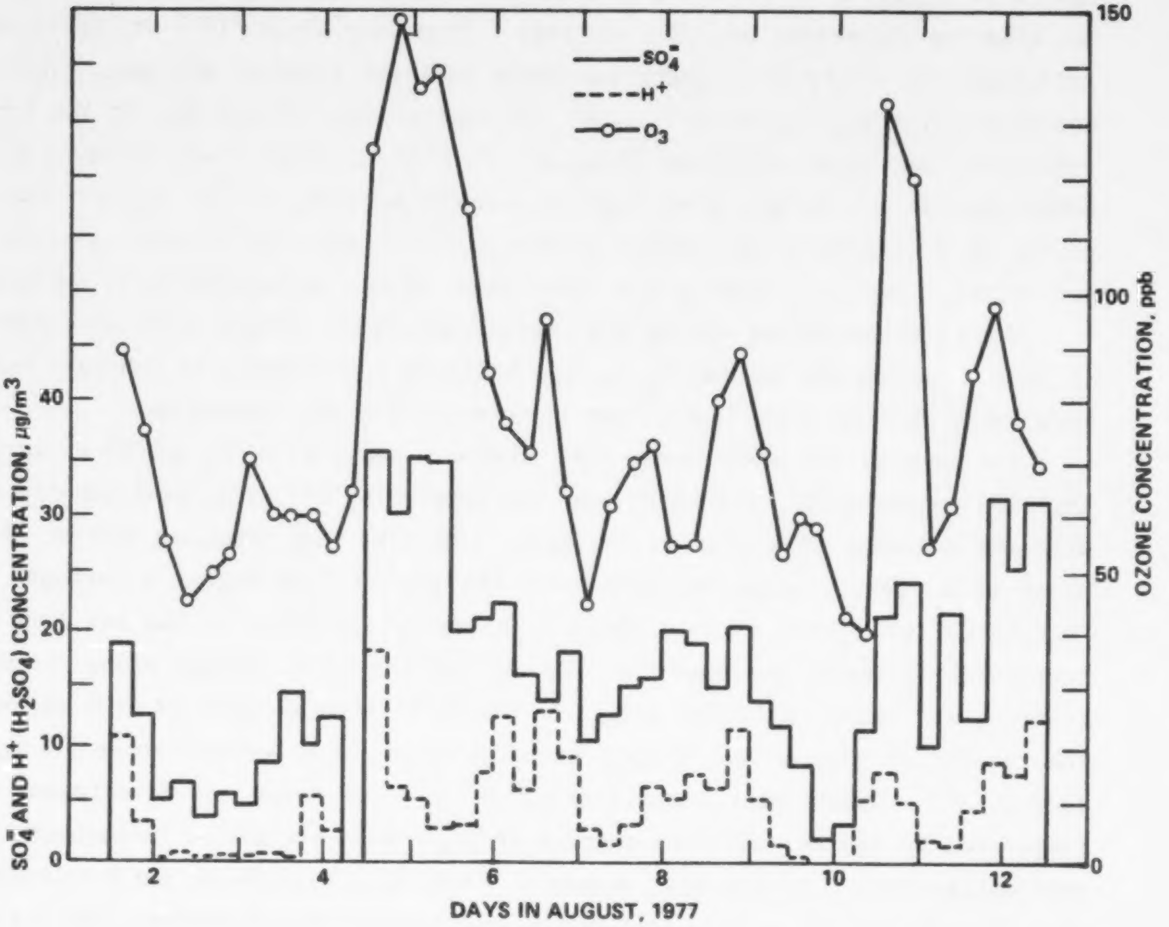


Figure 2-15. 6-hour $SO_4^=$ and H^+, and 6-hour max. O_3 samples collected during August, 1977 at High Point, NJ.

Source: Lioy and Waldman (1988).

neutralization and/or fresh acid production over the New York metropolitan area. Such changes in concentration suggested that complex relationships exist among SO_2 emissions, oxidation rates and the availability of NH_3.

Information on the regional nature of the acid in rural areas was also documented by Lioy et al. (1980) in comparisons with Pierson et al. (1980b) for events occurring at Allegheny Mountain, PA during the same period. On August 4, 1977 the levels of H^+ (as H_2SO_4) were 17.0 and 10.4 $\mu g/m^3$ for the periods 8 p.m. (August 3rd) to 8 a.m. (August 4th) and 8 a.m. to 8 p.m. (August 4th) respectively, which coincides with the peak observed at High Point, N.J. (320 km east). Similar coincidence observations of H^+ were found at both sites for the period August 6 through August 10. An independent study in Research Triangle Park, N.C. by Stevens et al. (1978) was conducted simultaneously with another part of the Pierson et al. (1980b) study. On July 31, 1977, the last day of the North Carolina study, the peak H^+ concentrations observed by Stevens et al. (1978) occurred simultaneously with an H^+ event at Allegheny Mountain, PA. The information from each comparison suggests that concentrations of acid in excess of 5 $\mu g/m^3$ occurred over extended periods for large segments of the Northeast during the summer of 1977.

The later studies by Stevens et al. (1980), in the Great Smokey Mountains, TN; by Stevens (1983) in the Shenandoah Valley, VA and by Lioy and Lippmann (1986) in Mendham, NJ again show the presence of acidic species in other nonurban areas within the Eastern U.S. Other results by Stevens (1983) indicated the presence of acidic species in Houston, TX, and were supported by semi-quantitative recent humidographic data from Waggoner et al. (1983).

In 1984 Spengler et al. (1986) initiated H_2SO_4 studies at two of the Harvard Six-Cities Health Study sites, Harriman, TN (coal burning area), and Watertown, MA (suburb of Boston). Using the FPD system for H_2SO_4 measurement they classified acid events. Data from their study shows the H_2SO_4 concentrations and the duration of events with H_2SO_4 >1 $\mu g/m^3$ for at least two hours (Table 2-9). This is a rather low threshold for classifying events, but the study gives one of the few comparisons of acidity in two different environments. Those that occurred in the coal burning area of Harriman, TN were of longer duration and higher concentration than at Watertown, MA. In Watertown, MA, the events were usually associated with regional transport conditions. In Harriman, TN, the events were associated with regional and local H_2SO_4 production. For both of these sites, the total strong acidity was probably underestimated since the ammonium bisulfate concentrations could not be measured by the FPD.

TABLE 2-9. ACID EVENTS (H_2SO_4 ≥1 μg/m^3 for ≤2 h)

	Watertown, Massachusetts (N = 72)		Harriman, Tennessee (N = 65)	
	Duration (hr)	Concentration (μg/m^3)	Duration (hr)	Concentration (μg/m^3)
MEAN	7.2	2.2	8.4	3.0
SD	5.2	1.4	6.4	1.5
75 percent	8.0	2.2	10.0	3.8
90 percent	17.7	4.4	17.4	4.7
MAX	24.0	7.4	41.0	9.5

N = Number of samples.

Source: Spengler et al. (1986).

In another investigation by Harvard (Ferris and Spengler, 1985) a high H_2SO_4 concentration (41 μg/m^3) was observed in St. Louis. In this case, wintertime conditions were studied, and the results suggested an association with power plant plumes.

A study by Appel et al., (1982) at Lennox in the Los Angeles basin was conducted for the period July 10 to July 17, 1979. A four hour maximum of 11 μg/m^3 of H_2SO_4 was observed on July 16 apparently associated with the daytime oxidation of local SO_2 emissions. Three other acid events were measured during this interval, although consistently high levels of SO_4^{-2} were measured throughout the sampling interval. Recently, a study was conducted by John et al. (1985) in Los Angeles in which the apparent H_2SO_4 was lower during this week-long study. They used two sites, and the downwind location, east of LA, recorded relatively high acid concentrations.

Cadle (1985) reported the results of acidity measurements (H^+) at a suburban site in Warren, MI from June 1981 through June 1982. The results were consistent with the growing body of information on apparent H_2SO_4. The most frequent excursions occurred during the summer with six 24 h samples exceeding 4 μg/m^3. However, the highest H_2SO_4 value occurred during the winter.

Two recent rural investigations, one in Whiteface Mt., NY (Kelly et al. 1985), and one in Nova Scotia, Canada (Smith-Palmer and Wentzell, 1986), focussed on acidic sulfate aerosol. In each case, there was at least one period during which the apparent H_2SO_4 concentration exceeded 9 μg/m^3.

To date, there have been a couple of studies in which the acid sulfate species were measured at two or more sites located <45 km apart (Waldman et al., 1987; Pierson et al., 1987). One study was conducted in Toronto, Canada during the summer of 1986 and on July 25th, H^+(as $H_2{}^+SO_4$) was observed at all three sites. The 8 h average peaks at each site were 8.3, 14.4, and 19.4 µg/m^3. The other study, the 1983 Allegheny-Laurel Experiment, was conducted at sites 36 km apart. Nine-hour average H^+ (as H_2SO_4) concentrations of 30 and 42 µg/m^3 were observed at these Pennsylvania sites on August 17, 1983 (Pierson et al., 1987).

The preceding discussion was limited to the data presently available on acid sulfate species. The studies were highly skewed to the summertime. Although large segments of the population could be affected by these regional acid events, seasonal profile of the types of situations where people could be exposed to high concentrations of acid species are not available (e.g., downwind of industrial and power plant plumes). The conditions conducive to high acid exposure in the other seasons must be examined, as well as the spatial distribution of acid sulfate (e.g., southeast and the mid-east during the winter).

The studies of Pierson et al. (1980b), Lioy et al. (1980), and Stevens et al. (1978) suggest that large areas of the northeast can be affected by acid aerosol during the summer. Recent work by Thurston and Waldman (1987) also suggest that these events can extend into Canada. Since the population potentially affected would be large, well focused studies on regional exposure to acid sulfate aerosol may be necessary.

2.7.2 Acid Sulfate Exposure and Events

The field studies described in the previous section measured a wide range of acid sulfate concentrations in the atmosphere. Most of the H_2SO_4 or H^+ (as H_2SO_4) values were below 5 µg/m^3, although events above 5 µg/m^3 occurred at least once over the course of each study. At present, there is no way to define an acid event systematically as an episode, since, as previously noted, periods of high acid sulfate do not necessarily coincide with periods of highest SO_4^{-2} concentrations; e.g., photochemical haze or smog. Therefore, the definition of an acid sulfate episode would be quite arbitrary. In the context of the following, a significant pollution excursion for acid sulfate will be defined as an event in which the measurement of free sulfuric acid or H^+ (as

H_2SO_4) reaches levels above 5 μg/m^3 for at least 1 h. No relationship to possible health effects is intended or implied in using the words significant, episode, or event and in some cases the exposure may be overestimated, e.g., 24 hrs, because the actual amount of time spent outdoors was not quantifiable in each study.

With the preceding criteria, some of the studies listed in Table 2-7 were selected for estimating the frequency of events, and the potential for exposure to acid sulfates as (μg/m^3)·h (Lioy and Waldman, 1988). It must be emphasized that the exposure (concentration x time) calculation will only be applied for determination of exposures that can occur during an event (annual average calculations of exposure are inappropriate). Event exposure calculations may be of some biological significance since it has been shown in a controlled human study that exposures to 100 μg/m^3 for more than one hour will yield enhanced effects, not additive effects, on mucocilliary clearance (Spektor et al., 1988; Schlesinger, 1988). For the purposes of the following discussion, however, the exposure values (μg/m^3)·h should be interpreted as the maximum potential exposure during an event, and not the biologically effective dose to an individual.

Because of the lack of a single approach to measuring acid sulfates, the studies examined in Table 2-10 have been grouped by sampling duration. In the case of studies with direct H_2SO_4 measurements the total hydrogen ion exposure will be underestimated, and in the case of studies with H^+ measurements the actual H_2SO_4 exposure probably will be overestimated.

The exposure and event results shown in Tables 2-10 through 2-15 and are divided into representative studies with sample collection times of 24 h, 12 h, 6 h 4 h, 1 h, and a combined sampling time (Lioy and Waldman, 1988). Unfortunately, the locations for the studies with the twelve hour samples, Table 2-11, and for the other sampling times, Table 2-12 through Table 2-15, were different from those examined for the 24-h studies, Table 2-10. Thus the results are not necessarily comparable spacially.

For the 24 h studies, Table 2-10, the events lasted a maximum of 24 h, which was the sample duration. This may be an underestimate of the length of the episode since the portion of the next or preceding 24-h period may have been above 5 μg/m^3 and could not have been detected. The exposures for the 24-h episodes ranged from 120 to 336 (μg/m^3)·h. For the day of the study, however, exposures were isolated instances of high acid sulfate.

TABLE 2-10. EPISODIC ACIDIC AEROSOL DATA AND ESTIMATES OF EXPOSURE FROM SELECTED ACID SULFATE CLASSIFIED BY SAMPLING TIME. ONLY PERIODS WHERE CONCENTRATIONS EXCEEDED 5 μg/m³ OF APPARENT H_2SO_4 ARE USED AS EVENTS
24 HOUR DATA

Study (Period)	Date	Peak (μg/m³)	Mean (μg/m³)	Exposure (μg/m³)·h
Whiteface Mt.*	1984			
(85 samples	July	8.2	8.2	197
collected	August	10.0	10.0	240
over 1 yr)	August	14.0	14.0	336
Nova Scotia**	1983			
(23 days)	September 6	9.0	9.0	216
Warren, MI***	1981			
(1 yr)	July	9.0	9.0	216
	July	6.5	6.5	156
	July	7.5	7.5	180
	July	6.7	6.7	160
	August	5.0	5.0	120
	August	5.0	5.0	120
	November	6.5	6.5	156
	February	10.0	10.0	240
St Louis, MO****	1985/1986			
(9 months)	September	6.1	6.1	146
Kingston, TN****	1985/1986			
(9 months)	May 30	7.7	7.7	184
	June 3	5.9	5.9	141
	July 6	5.4	5.4	135
	July 17	10.6	11.1	509
	July 22	8.0	8.3	384
	August 5	6.1	6.1	146
	August 18	14.3	14.3	343

*Kelly et al. (1985).

**Smith-Palmer and Wentzell (1986).

***Cadle (1985).

****Koutrakis et al. (1987).

The acid sulfate events for the 12-h samples reached 36-h in duration and recorded peak exposures of 510 and 925 (μg/m³)·h. An interesting feature of the 12-h studies was that each was conducted for a period of one month or less, and each had at least one event with acidic sulfate exposure above 100 (μg/m³)·h. Obviously, the frequency of acid events can not be described in this analysis, since longer studies would be required in each location.

TABLE 2-11. TWELVE HOUR ACID AEROSOL DATA AND ESTIMATES OF EXPOSURE

Study	Date	Peak (μg/m³)	Mean (μg/m³)	Duration (h)	Exposure (μg/m³)·h
Tuxedo, NY*	1980				
(31 days)	August 2	8.0	8.0	12	97
	August 8	8.0	8.0	12	97
	August 27	20.1	14.2	36	511
Glasgow, IL**	1975				
(8 days)	July 22	9.3	9.3	12	112
	July 26	5.2	5.2	12	62
	July 28, 29	36.0	25.7	36	925
Smokey Mts***	1978				
(6 days)	September 20-21	5.6	5.6	12	68
	September 21-22	8.2	8.2	12	98
	September 24-26	9.6	8.6	36	308
Houston, TX****	1980				
(9 days)	September 11	6.4	6.4	12	76
	September 12	6.7	6.7	12	81
	September 13	7.6	7.6	12	91

*Morandi et al. (1983).

**Tanner et al. (1977).

***Stevens et al. (1978).

****Stevens (1983).

TABLE 2-12. SIX HOUR ACID AEROSOL DATA AND ESTIMATES OF EXPOSURE

Study	Date	Peak (μg/m³)	Mean (μg/m³)	Duration (h)	Exposure (μg/m³)·h
High Point, NJ*	1977				
(11 days)	August 1	11.6	11.6	6	69
	August 3	5.8	5.8	6	35
	August 4-5	17.6	9.0	24	215
	August 5-6	13.8	10.1	30	304
	August 7-9	11.6	7.4	36	264
	August 10	8.2	6.5	18	118
	August 11-12	12.6	8.3	24	198
Shenandoah Valley**	1980				
(7 days)	August 29-September 1	21.3	14.6	24	350

*Lioy et al. (1980).

**Stevens (1983).

TABLE 2-13. FOUR HOUR ACID AEROSOL DATA AND ESTIMATES OF EXPOSURE

Study	Date	Peak ($\mu g/m^3$)	Mean ($\mu g/m^3$)	Duration (h)	Exposure ($\mu g/m^3$)·h
RTP, NC*	1977				
(3.5 days)	July 31	12.3	6.9	4	27
Lennox, CA**	1979				
(8 days)	July 15	8.1	8.1	2 (2h average)	16
	July 16	10.9	10.9	4	42

*Stevens et al. (1978).

**Appel et al. (1982).

TABLE 2-14. ONE HOUR ACID AEROSOL DATA AND ESTIMATES OF EXPOSURE

Study	Date	Peak ($\mu g/m^3$)	Mean ($\mu g/m^3$)	Duration (h)	Exposure ($\mu g/m^3$)·h
St. Louis, MO*	1977				
(61 days)	July 15	12.2	7.0	3	21
	July 16-17	18.4	9.2	7	64
	July 17	27.6	13.0	4	52
(59 days)	1978				
	February 9-10	10.5	7.0	13	91
	February 10	8.0	6.0	1	6
	February 10	9.0	7.0	3	21
	February 11	9.0	7.5	4	30
	February 11	13.7	8.5	20	170
St. Louis, MO**	1984				
(8 days)	August 4	7.4	7.4	1	7
	August 5	9.8	9.8	1	10
	August 6	7.4	7.4	1	7
	August 7	12.3	12.3	1	12
	August 8	8.3	8.3	1	8
Harriman, TN***	1984				
(7 days)	August 13	8.0	6.0	7	42
	August 14	10.0	6.5	13	85
	August 15	18.0	8.5	16	136
	August 16	9.0	6.3	4	25
	August 17	7.0	5.8	5	29
	August 18	14.0	8.0	11	88
	August 19	6.0	5.2	2	10

(continued on the following page)

TABLE 2-14. (continued)

Study	Date	Peak ($\mu g/m^3$)	Mean ($\mu g/m^3$)	Duration (h)	Exposure ($\mu g/m^3$)·h
Watertown, MA***	1984				
(7 days)	August 9	14.0	7.0	6	42
	August 10	14.0	7.5	12	90
	August 12	11.0	7.0	8	56

*Cobourn (1979).

**Cobourn and Husar (1982).

***Spengler et al. (1986).

TABLE 2-15. FOUR-, EIGHT- AND SIXTEEN-HOUR ACID AEROSOL DATA AND ESTIMATES OF EXPOSURE

Study		Date	Peak ($\mu g/m^3$)	Mean ($\mu g/m^3$)	Duration (h)	Exposure ($\mu g/m^3$)·h
Toronto		1986				
(6 weeks)	(Site 1)	July 19	7.8	6.4	13.4	86
	(Site 1)	July 25	14.4	14.1	18.8	264
	(Site 2)	July 25	19.4	13.4	25.3	338
	(Site 3)	July 25	8.3	8.3	7.5	62

Source: Waldman et al. (1987).

The 6 h analyses yielded information similar to the 12 h samples since the two examples had calculated exposures above 100 ($\mu g/m^3$)·h during intervals of sampling that encompassed less than two weeks. However, the intensity and duration of the High Point, N.J. (Lioy et al., 1980) exposures were quite different. In the period from August 5 through 12 there were almost continuous exposures to acidic sulfate above 100 ($\mu g/m^3$)·h. On some of the days there were 6 h periods when H^+ (as H_2SO_4) was not above 5 $\mu g/m^3$, but these were the exception rather than the rule.

The 4-h data are limited to two studies, (Table 2-13) Research Triangle Park, N.C. (Stevens et al. 1978), and Lennox, CA (Appel et al., 1982). There were no acid exposures above 100 ($\mu g/m^3$)·h in either case. General conclusions on the absence of acid sulfate episodes in these instances can not be drawn, since the duration of the programs were less than two weeks.

The examples of 1-h sample studies, all of which made direct H_2SO_4 measurements showed the duration of an acid episode ranging from 1 to 20 h.

In contrast to the locations examined previously, there were only two instances during which exposures to H_2SO_4 were above 100 ($\mu g/m^3$)·h and three above 80 ($\mu g/m^3$)·h. In the case of St. Louis, this was puzzling, since the sampling included an entire year, and there are major sources of SO_2 in the area (Husar et al., 1978). The work, however, of Ellestad (1980) and the previously cited work of Tanner and Marlow (1977) may explain part of this lack of frequent high excursions in H_2SO_4. Even though St. Louis has major sources of SO_2, the main impact was probably at some distance downwind. During the 1975 Midwest Interstate Sulfur Transformation and Transport (MISST) study at Glasgow, IL, Ellestad (1980) measured particle light scattering downwind of the St. Louis urban and power plant plumes and found aerosol production during the summer. The Tanner and Marlow (1977) summertime H^+ measurements indicated very high exposures (>900 $\mu g/m^3$·h) at this same location. Thus the main acid impact from the plume in this case was downwind. In the future, studies will require careful consideration of where major plume impacts will occur, and their potential for producing high acid concentrations and exposures.

In the Toronto, Canada study, Waldman et al. (1987) used a scheme which involved collection of samples for a variety of time intervals, depending on whether a sulfate episode was in progress-see Table 2-15 (Thurston and Waldman, 1987). The exposure analyses completed for the three sites across a metropolitan area of 2.5 million people showed that there was one period, July 25th, during which exposures at two of the three sites were above 100 ($\mu g/m^3$)·h. At the third site, the levels were much lower, probably because of local neutralization. Thus, the potential for local differences in acid sulfate is present and will have to be examined in the future to assess where maximum exposures occur.

Research recently conducted at Camp Kiawa in Southern Ontario by Spengler et al. (1988) considered exposure to acids on a 12-h basis for H^+ and as 1-h averages for H_2SO_4. For the same event described by Thurston and Waldman (1987), a 1-h maximum of sulfuric acid of 50 $\mu g/m^3$ was measured at the camp. The entire 36-h event had measured 12-h sequential H^+ (as H_2SO_4) of 120, 336, and 150 ($\mu g/m^3$)·h. A delivered dose to the lung of 52 µg was calculated for the peak 1-h acid concentration on July 25, 1986.

2.7.3 Atmospheric Nitric Acid Concentration

Ambient data on nitric acid in the atmosphere are available from Spicer et al. (1982) for Claremont, CA, Figure 2-16. Another study conducted in

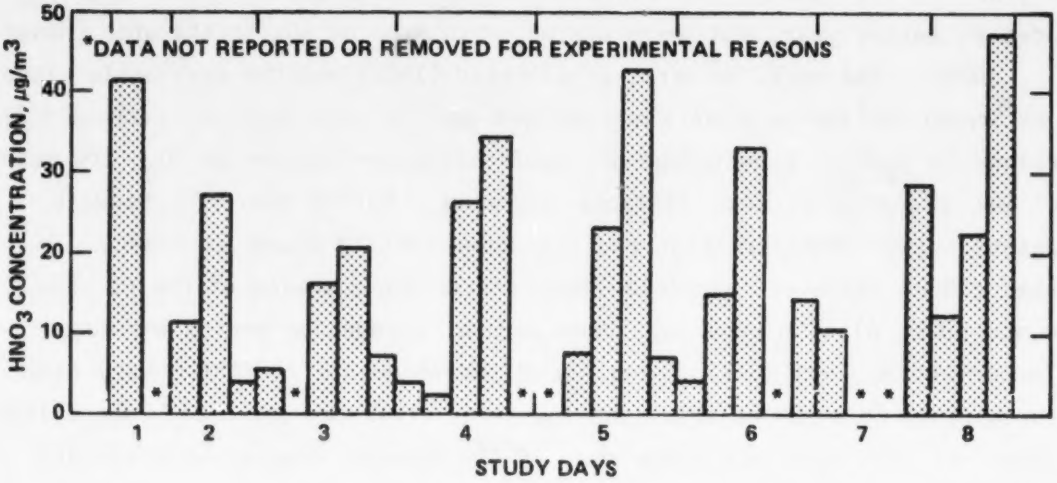


Figure 2-16. Nitric acid measurements taken at Claremont, CA, August and September 1979.

Source: Spicer et al. (1982).

Los Angeles, California by Sickles (1986) measured levels of nitric acid that ranged from 0.2 to 32 µg/m^3. By way of comparison, data collected in in the Ohio Valley and in North Carolina are shown in Table 2-16 and Figure 2-17. The results from these locations, which were obtained in a different time of the year, indicate much higher concentration of HNO_3 in California. Other data taken by Spicer et al. (1978) during the summer in St. Louis, MO showed maximum concentrations in excess of 30 µg/m^3 for 23 h and 200 µg/m^3 for 1 h.

2.8 SUMMARY

The level of knowledge about the frequency, magnitude and duration of acid sulfate particle events/episodes is insufficient. Efforts must be made to gather more data, but these should be done in such a way that situations where maximum human exposures may occur are the focus of the research. In addition,

TABLE 2-16. RESULTS OF COLUMBUS AMBIENT AIR SAMPLING

Date	Day Of Week	Total Inorganic Nitrates (μg/m^3)	NO_3^- (μg/m^3)	HNO_3 (μg/m^3)	SO_4^{-2} (μg/m^3)	HCl (μg/m^3)
10-17-79	W	0.30	0.30	<0.30	<0.30	-
10-18-79	Th	2.40	1.10	1.31	1.01	-
10-19-79	F	3.40	2.16	1.24	14.02	-
10-20/22-79	S-M	1.90	1.07	0.82	0.87	-
10-22/23-79	M-Tu	1.26	0.78	0.48	0.60	-
10-23-79	Tu	<0.50	<0.50	<0.50	2.52	-
10-24-79	W	3.43	3.10	0.33	3.31	-
10-25-79	Th	3.37	2.36	1.01	0.56	-
10-26-79	F	2.10	0.60	1.50	0.78	-
10-27/28-79	S-S	4.66	3.00	1.66	3.80	-
10-29-79	M	7.83	3.15	4.67	0.76	-
10-30-79	Tu	5.39	2.04	3.35	4.49	-
10-31-79	W	2.28	0.54	1.74	2.57	-
11-2-79	F	3.11	2.22	0.90	2.75	-
11-19-79	M	2.32	0.65	1.67	1.84	-
11-28-79	W	2.11	1.53	0.59	0.53	-
12-4-79	Tu	3.29	2.28	1.02	1.08	-
12-11-79	Tu	1.92	0.78	1.14	0.72	-
12-18-79	Tu	2.81	2.51	0.30	3.65	-
1-3-80	Th	2.57	1.20	1.38	0.84	-
1-8-80	Tu	3.89	3.41	0.48	3.05	-
1-16-80	W	1.68	0.54	1.14	15.27	-
1-21-80	M	5.92	5.15	0.77	3.90	-
1-28-80	M	7.86	6.43	1.43	4.40	-
2-11-80	M	4.97	3.21	1.76	7.15	-
2-19-80	Tu	3.89	1.61	2.28	1.09	-
2-25-80	M	4.59	3.92	0.67	6.18	-
3-3-80	M	2.66	0.36	2.31	2.01	-
3-10-80	M	1.06	0.47	0.59	0.47	-
3-17-80	M	4.32	3.30	1.02	0.51	-
3-24-80	M	2.14	0.68	1.46	5.63	-
3-31-80	M	3.06	1.15	1.91	0.33	-
4-9-80	W	9.54	9.17	0.38	2.27	-
4-14-80	M	1.43	0.29	1.14	<0.28	-
4-21-80	M	2.80	0.96	1.85	<0.32	-
4-28-80	M	5.03	3.62	1.41	1.58	-
5-12-80	M	4.20	2.72	1.48	3.64	-
5-21-80	W	9.26	1.48	7.78	12.41	-
5-28-80	W	7.78	2.09	5.69	2.94	-
6-3-80	Tu	3.54	0.90	2.64	3.36	-
6-9-80	M	1.57	0.82	0.75	0.88	-
6-14/15-80	S-S	4.66	1.55	3.10	6.52	-
6-23-80	M	6.79	2.32	4.46	12.32	-
6-30-80	M	2.03	0.70	1.33	1.12	-
7-7-80	M	3.99	1.44	2.54	3.76	-
7-8-80	Tu	4.24	1.98	2.27	3.72	-

(continued on the following page)

TABLE 2-16. (continued)

Date	Day Of Week	Total Inorganic Nitrates (μg/m³)	NO_3^- (μg/m³)	HNO_3 (μg/m³)	SO_4^{-2} (μg/m³)	HCl (μg/m³)
8-12-80	Tu	3.27	1.06	2.43	0.40	-
8-25-80	M	8.92	5.24	3.67	31.20	-
9-2-80	Tu	4.35	3.66	0.68	9.69	0.25
9-11-80	Th	3.84	2.20	1.64	5.54	1.41
9-15-80	M	2.17	1.58	0.60	5.16	1.52
9-22-80	M	1.77	0.96	0.81	1.16	0.05
9-30-80	Tu	2.40	1.43	0.97	6.04	0.39
10-5-80	M	4.20	3.19	1.01	7.13	0.21
10-15-80	W	4.11	2.38	1.73	5.30	0.54
10-21-80	Tu	3.88	2.52	1.35	2.23	0.18
10-29-80	W	1.79	1.42	0.37	1.73	0.25

Source: Spicer (1986).

further data are required on the mechanisms of formation of H_2SO_4, and on what factors can be used to predict acid sulfate episodes. The motivation for conducting more studies is primarily the potential for an effect and the establishment of the conditions for exposure. The high exposures calculated for some of the documented data were not for studies necessarily designed to examine high as well as low human exposures. Most were basically designed to investigate the characteristics of the atmosphere. Thus higher exposure situations could be present in North America.

From the studies identified and discussed, it appears that two potential exposure situations are possible. Those related to: (1) regional stagnation and transport conditions, and (2) local plume impacts.

Levels of apparent H_2SO_4 in excess of 20 to 40 $\mu g/m^3$ have been observed for time durations ranging from 1 to 12 hours, and these were associated with atmospheric SO_4^{-2} levels in excess of 40 $\mu g/m^3$ and with possible exposures during episodes of >900 $(\mu g/m^3) \cdot h$. Earlier London studies indicated that H_2SO_4 in excess of 100 $\mu g/m^3$ can be present in the atmosphere, and exposures >2,000 $(\mu g/m^3) \cdot h$ were possible.

It is apparent that the two types of outdoor conditions mentioned above can lead to a number of possible situations for conducting epidemiological and human exposure studies. The first would be studies conducted during major summertime haze episodes, where large populations in the eastern U.S. could

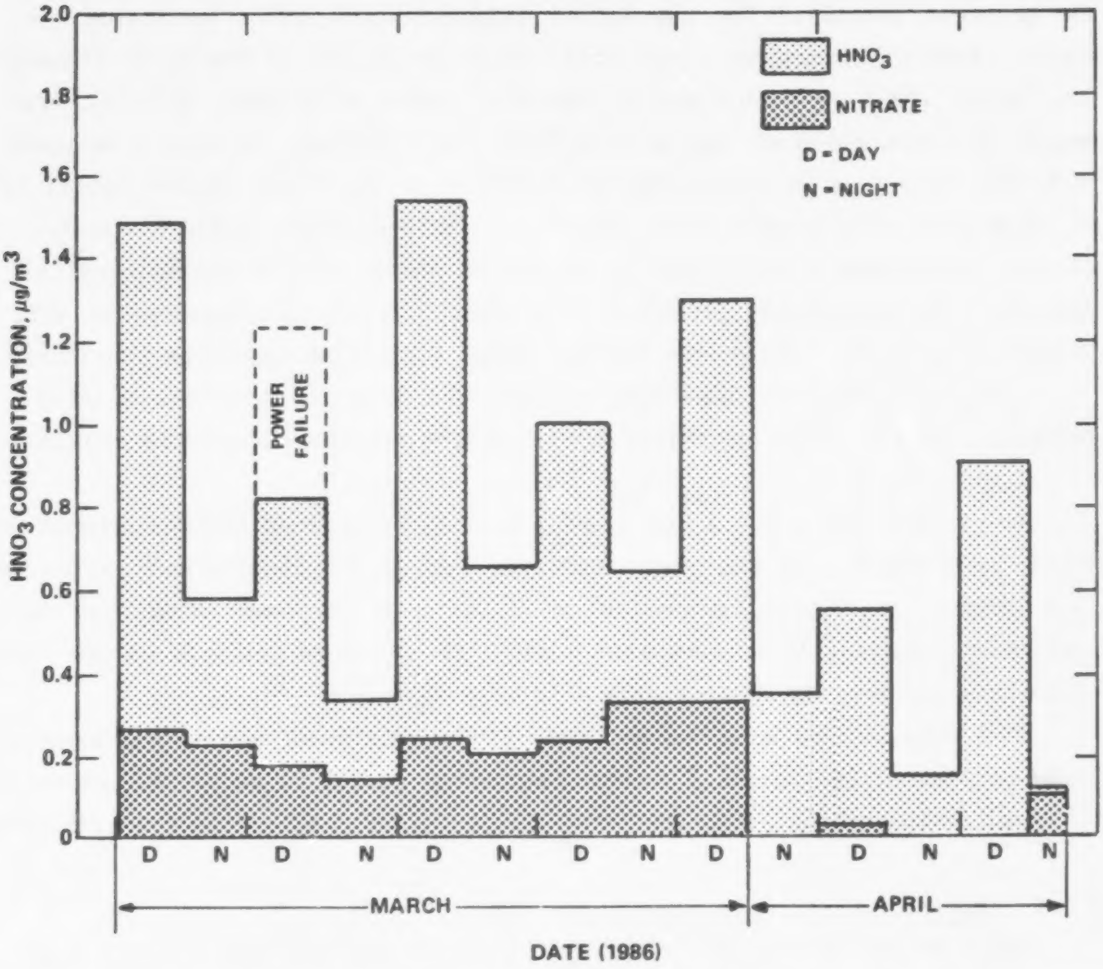


Figure 2-17. Diurnal variation in nitrate concentration, Raleigh, NC, 1985.

Source: Stevens (1986).

be affected periodically by high acid sulfate levels. The exposure could be manifested by high H_2SO_4 and/or NH_4HSO_4 accumulated over periods of one hour or more throughout a day or sequence of days. Because these episodes occur in the summer, large segments of the population will be participating in outdoor activities in the rural and suburban areas. These individuals would be most at risk during regional events, and would be the focus of opportunities for epidemiological studies.

The second type of exposure would be confined to places downwind of a power plant plume or urban plume during any season of the year. Obviously, the greatest potential for population exposure would still be during the summer; however, exposures could still occur during all of the other seasons. The latter would be confounded by variable levels of outdoor activity, and degree of penetration of the acid sulfate into the home. It should be noted that the highest acid concentrations observed in the cited studies appear to be associated with direct plume impacts. Therefore, these types of locations warrant considerable attention in long-term health effect epidemiological studies. In considering locations for investigations on exposures to acid aerosols, locations outside the United States and Canada should be considered.

Space heating with open heat sources can lead to emissions of acid aerosols indoors. This potential acid exposure situation should be considered for study.

At present there are a few studies that have included the measurement of nitric acid vapor. As the use of samplers such as the annular denuder become more common, the concentrations of the H^+ in both the vapor phase and the particulate phase will be more easily compared. Further research on the techniques for nitric acid determinations is also necessary.

Most research on acid fog has been limited to rural and in mountainous areas outside of California. A better data base on fog is necessary, especially in terms of the potential for enhanced aerosol acidity after the fog evaporates.

2.8.1 Implications for Atmospheric Pollution Studies

Many of the technique limitations and the implications derived from measurement of strong acids in atmospheric aerosols have already been introduced in the preceding sections. A summary of these limitations and implications is included below.

1. Most of the strong acid content of the atmospheric aerosol derives from partially NH_3-neutralized sulfuric acid aerosol.

2. Regional levels of acid sulfate aerosols are predominantly formed by secondary oxidation processes in the atmosphere, with only a small fraction from primary emissions.

3. Techniques now exist that are in large part sufficiently sensitive and selective for ambient measurements with adequate time resolution for surface measurements. Improvements are still needed for certain airborne applications.

4. No practical technique exists that distinguishes ammonium bisulfate from ammonium sulfate in either internal or external mixtures in ambient aerosols.

5. Local ammonia concentrations largely control the surface levels of atmospheric strong acids to which populations are exposed. Additional measurements of this important species are recommended.

2.9 REFERENCES

Allen, G. A.; Turner, W. A.; Wolfson, J. M.; Spengler, J. D. (1984) Description of a continuous sulfuric acid/sulfate monitor. Presented at: the 4th national symposium on recent advances in pollutant monitoring of ambient air and stationary sources; May; Raleigh, NC.

Appel, B. R.; Tokiwa, T.; Wall, S. M.; Haik, M.; Kothny, E. L.; Wesolowski, J. J. (1979) Determination of sulfuric acid, total particle-phase acidity and nitric acid in ambient air. Berkeley, CA: Air and Industrial Hygiene Laboratory; report no. CA/DOH/AIHL/SP-18.

Appel, B. R.; Wall, S. M.; Haik, M.; Kothny, E. L.; Tokiwa, Y. (1980) Evaluation of techniques for sulfuric acid and particulate strong acidity measurements in ambient air. Atmos. Environ. 14: 559-563.

Appel, B. R.; Hoffer, E. M.; Tokiwa, Y.; Kothny, E. L. (1982) Measurement of sulfuric acid and particulate strong acidity in the Los Angeles basin. Atmos. Environ. 16: 589-593.

Askne, C.; Brosset, C. (1972) Determination of strong acid in precipitation, lake-water and air-borne matter. Atmos. Environ. 6: 695-696.

Baboolal, B.; Pruppacher, H. R.; Topalian, J. H. (1981) A sensitivity study of a theoretical model of SO_2 scavenging by water drops in air. J. Atmos. Sci. 38: 856-870.

Barton, S. C.; McAdie, H. G. (1971) A specific method for the automatic determination of ambient H_2SO_4 aerosol. In: Englund, H. M.; Beery, W. T., eds. Proceedings of the second international clean air congress; December 1970; Washington, DC. New York, NY: Academic Press, Inc.; pp. 379-382.

Beck, W. B.; Tannahill, G. K. (1978) An overview of the Houston area oxidant study. Presented at: 71st annual meeting of the Air Pollution Control Association; June; Houston, TX. Pittsburgh, PA: Air Pollution Control Association; paper no. 78-30.1.

Brewer, R. L.; Gordon, R. J.; Shepard, L. S.; Ellis, E. C. (1983) Chemistry of mist and fog from the Los Angeles urban area. Atmos. Environ. 17: 2267-2270.

Brosset, C.; Ferm, M. (1978) Man-made airborne acidity and its determination. Atmos. Environ. 12: 909-916.

Brosset, C.; Andreasson, K.; Ferm, M. (1975) The nature and possible origin of acid particles observed at the Swedish west coast. Atmos. Environ. 9: 631-642.

Cadle, S. H. (1985) Seasonal variations in nitric acid, nitrate, strong aerosol acidity, and ammonia in an urban area. Atmos. Environ. 19: 181-188.

Camp, D. C. (1980) An intercomparison of results from samplers used in the determination of aerosol composition. Environ. Int. 4: 83-100.

Camp, D. C.; Stevens, R. K.; Cobourn, W. G.; Husar, R. B. (1982) Intercomparison of concentration results from fine particle sulfur monitors. Atmos. Environ. 16: 911-916.

Castillo, R. A.; Jiusto, J. E.; McLaren, E. (1983) The pH and ionic composition of stratiform cloud water. Atmos. Environ. 17: 1497-1505.

Chang, S. G.; Brodzinsky, R.; Tousi, R.; Markowitz; Novakon,T. (1979) Catalytic oxidation of carbon in aqueous solutions. In: Proceedings: carbonaceous particles in the atmosphere; Berkeley, CA: Lawrence Berkeley Laboratory; University of California; pp. 122-130; LBL report no. LBL-9037.

Charlson, R. J.; Vanderpol, A. H.; Covert, D. S.; Waggoner, A. P.; Ahlquist, N. C. (1974) $H_2SO_4/(NH_4)_2SO_4$ background aerosol - optical detection in St. Louis region. Atmos. Environ. 8: 1257-1257.

Charlson, R. J.; Covert, D. S.; Larson, T. V.; Waggoner, A. P. (1978) Chemical properties of tropospheric sulfur aerosols. Atmos. Environ. 12: 39-53.

Cobourn, W. G. (1979) In-situ measurements of sulfuric acid and sulfate aerosol in St. Louis [dissertation]. St. Louis, MO: Washington University. Available from: University Microfilms, Ann Arbor, MI; publication no. AAD80-19160.

Cobourn, W. G.; Husar, R. B. (1982) Diurnal and seasonal patterns of particulate sulfur and sulfuric acid in St. Louis, July 1977-June 1978. Atmos. Environ. 16: 1441-1450.

Cobourn, W. G.; Husar, R. B.; Husar, J. D. (1978) Continuous in situ monitoring of ambient particulate sulfur using flame photometry and thermal analysis. Atmos. Environ. 12: 89-98.

Commins, B. T. (1963) Determination of particulate acid in town air. Analyst (London) 88: 364-367.

Commins, B. T.; Waller, R. E. (1967) Observations from a ten-year study of pollution at a site in the city of London. Atmos. Environ. 1: 49-68.

Coutant, R. W. (1977) Effect of environmental variables on collection of atmospheric sulfate. Environ. Sci. Technol. 11: 873-878.

Cunningham, P. T.; Johnson, S. A. (1976) Spectroscopic observation of acid sulfate in atmospheric particulate samples. Science (Washington, DC) 191: 77-79.

D'Ottavio, T.; Garber, R.; Tanner, R. L.; Newman, L. (1981) Determination of ambient aerosol sulfur using a continuous flame photometric detection system. II. The measurement of low-level sulfur concentrations under varying atmospheric conditions. Atmos. Environ. 15: 197-203.

Dubois, L; Baker, C. J.; Teichman, T.; Zdrojewski, A.; Monkman, J. L. (1969) The determination of sulphuric acid in air: a specific method. Mikrochim. Acta (Wien): 269-279.

Dutkiewicz, V. A.; Halstead, J. A.; Parekh, P. P.; Khav, A.; Husain, (1983) Anatomy of an episode of high sulfate concentrations at Whiteface Mountain, NY. Atmos. Environ. 8: 1475-1482.

Dzubay, T. G.; Snyder, G. K.; Reutter, D. J.; Stevens, R. K. (1979) Aerosol acidity determination by reaction with 14-C labelled amine. Atmos. Environ. 13: 1209-1212.

Eatough, D. J.; Izatt, S.; Ryder, J.; Hansen, L. D. (1978) Use of benzaldehyde as a selective solvent for sulfuric acid: interferences by sulfate and sulfite salts. Environ. Sci. Technol. 12: 1276-1279.

Ellestad, T. G. (1980) Aerosol composition of urban plumes passing over a rural monitoring site. Ann. N. Y. Acad. Sci. 338: 202-218.

Falconer, P. D., ed. (1981) Cloud chemistry and meteorological research at Whiteface Mountain: summer 1980. Albany, NY: State University of New York, Atmospheric Sciences Research Center; publication no. 806.

Ferek, R. J.; Lazrus, A. L.; Haagenson, P. L.; Winchester, J. W. (1983) Strong and weak acidity of aerosols collected over the northeastern United States. Environ. Sci. Technol. 17: 315-324.

Ferris, B. G., Jr.; Spengler, J. D. (1985) Problems in estimation of human exposure to components of acid precipitation precursors. EHP Environ. Health Perspect. 63: 5-9.

Firket, J. (1936) Fog along the Meuse Valley. Trans. Faraday Soc. 32: 1102-1197.

Friedlander, S. K. (1980) Future aerosols of the southwest. In: Kneip, T. J.; Lioy, P. J., eds. Aerosols: anthropogenic and natural sources and transport. Ann. N. Y. Acad. Sci. 338: 588-598.

Fujita, E.; Amar, P.; Ashbaugh, L.; Walker, W.; Tonnessen, K.; Ahuja, M.; Westerdahl, D. (1986) The fourth annual report to the governor and the legislature on the Air Resources Board's acid deposition research and monitoring program. Sacramento, CA: State of California Air Resources Board, Acid Deposition and Aerosol Research Section.

Fuzzi, S.; Castillo, R. A.; Juisto, J. E.; Lala, G. G. (1984) Chemical composition of radiation fag water at Albany, N. Y. and the relationship to fog microphysics. J. Geophys. Res. D.: Atmos. 89D: 7159-7164.

Galvin, P. J.; Samson, P. J.; Coffey, P. E.; Romano, D. (1978) Transport of sulfate to New York State. Environ. Sci. Technol. 12: 580-584.

Gillani, N. V.; Colby, J. A.; Wilson, W. E. (1983) Gas-to-particle conversion of sulfur in power plant plumes-- III. Parameterization of plume-cloud interactions. Atmos. Environ. 17: 1753-1763.

Gillani, N. V.; Kohli, S.; Wilson, W. E. (1981) Gas-to-particle conversion of sulfur in power plant plumes-- I. Parameterization of the conversion rate for dry, moderately polluted ambient conditions. Atmos. Environ. 15: 2293-2313.

Haines, B.; Stefani, M.; Hendrix, F. (1980) Acid rain: threshold of leaf damage in eight plant species from a southern Appalachian forest succession. Water Air Soil Pollut. 14: 403-407.

Hegg, D. A.; Hobbs, P. V. (1981) Cloud water chemistry and the production of sulfates in clouds. Atmos. Environ. 15: 1597-1604.

Hegg, D. A.; Hobbs, P. V. (1982) Measurements of sulfate production in natural clouds. Atmos. Environ. 16: 2663-2668.

Hering, S. V. (1986) The nitric acid shootout: field comparison of measurement methods. Los Angeles, CA: University of California at Los Angeles, Chemical Engineering Dept.; CARB contracts A4-164-32 and A5-068-32.

Hidy, G. M. (1986) Definition and characterization of suspended particles in ambient air. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment and control strategies: proceedings of the second U. S.-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 19-41.

Hidy, G. M.; Mueller, P. K.; Tong, E. Y. (1978) In: Husar, R. B.; Lodge, J. P.; Moore, D. J., eds. Spatial and temporal distributions of airborne sulfate in parts of the United States, sulfur in the atmosphere. Pergamon Press; pp. 735-752.

Hidy, G. M.; Mueller, P. K.; Grosjean, D.; Appel, B. R.; Wesolowski, J. J., eds. (1980) The character and origins of smog aerosols: a digest of results from the California Aerosol Characterization Experiment (ACHEX). New York, NY: John Wiley and Sons.

Hoffmann, M. R. (1984) Comment on "acid fog" [reply]. Environ. Sci. Technol. 18: 61-64.

Houghton, H. G. (1955) J. Meteorol. 12: 355-357.

Huntzicker, J. J.; Hoffman, R. S.; Ling, C.-S. (1978) Continuous measurement and speciation of sulfur-containing aerosols by flame photometry. Atmos. Environ. 12: 83-88.

Huntzicker, J. J.; Hoffman, R. S.; Cary, R. A. (1984) Aerosol sulfur episodes in St. Louis, Missouri. Environ. Sci. Technol. 18: 962-967.

Husar, R. B. (1982) Ammonia over North America: sources, sinks, and flow rates. St. Louis, MO: CAPITA, Washington University.

Husar, R. B.; Holloway, J. M. (1983) Sulfur and nitrogen over North America. In: Ecological effects of acid deposition: report and background papers 1982 Stockholm conference on the acidification of the environment, expert meeting I. Stockholm, Sweden: National Swedish Environment Protection Board; report PM 1636; pp. 95-115.

Husar, R. B.; Lodge, J. P., Jr.; Moore, D. J., eds. (1978) Sulfur in the atmosphere: proceedings of the international symposium; September 1977; Dubrovnik, Yugoslavia. Atmos. Environ. 12(1-3).

Huygen, C. (1975) A simple photometric determination of sulphuric acid aerosol. Atmos. Environ. 9: 315-319.

Ito, K.; Thurston, G. D. (1987) The estimation of London England aerosol exposures from historical visibility records. Presented at: 80th annual meeting of the Air Pollution Control Association; New York, NY. Pittsburgh, PA: Air Pollution Control Association; paper no. 87-42.2.

Jacob, D. J.; Waldman, J. M.; Munger, J. W.; Hoffmann, M. R. (1984) A field investigation of physical and chemical mechanisms affecting pollutant concentrations in fog droplets. Tellus Ser. B 36B: 272-285.

Jacob, D. J.; Waldman, J. M.; Munger, J. W.; Hoffmann, M. R. (1985) Chemical composition of fogwater collected along the California coast. Environ. Sci. Technol. 19: 730-736.

John, W.; Wall, S. M.; Ondo, J. L. (1985) Dry acid deposition on materials and vegetation: concentration in ambient air. California Air Resources Board Interagency agreement A1-160-32.

Junge, C.; Scheich, G. (1971) Determination of the acid content of aerosol particles. Atmos. Environ. 5: 165-175.

Keeler, G. J. (1987) A hybrid approach for source apportionment of atmospheric pollutants in the north eastern United States [disseration]. Ann Arbor, MI: University of Michigan.

Keene, W. C.; Galloway, J. N. (1985) Gran's titrations: inherent errors in measuring the acidity of precipitation. Atmos. Environ. 19: 199-202.

Kelly, T. J.; Tanner, R. L.; McLaren, S. E.; DuBois, M. V. (1985) Seasonal variations in atmospheric chemistry in the Adirondacks. Presented at: 78th annual meeting of the Air Pollution Control Association; June; Detroit, MI. Pittsburgh, PA: Air Pollution Control Association; paper no. 85-7.5.

Klockow, D.; Richter, M.; Niessner, R. (1982) Combination of diffusion separation and chemiluminescence detection for collection and selective determination of airborne nitric acid. Presented at: the 12th annual symposium on the analytical chemistry of pollutants; April; Amsterdam, The Netherlands.

Koutrakis, P. E.; Wolfson, J. M.; Spengler, J. D. (1987) An improved method for measuring aerosol strong acidity; results from a nine-month study in St. Louis, Missouri and Kinston, Tennessee. Atmos. Environ. 24: 1-6.

Krupa, S.; Coscio, M. R., Jr.; Wood, F. A. (1976) Evaluation of a coulometric procedure for the detection of strong and weak acid components in rainwater. J. Air Pollut. Control Assoc. 26: 221-223.

Larson, T. V.; Ahlquist, N. C.; Weiss, R. E.; Covert, D. S.; Waggoner, A. P. (1982) Chemical speciation of H_2SO_4-$(NH_4)_2SO_4$ particles using temperature and humidity controlled nephelometry. Atmos. Environ. 16: 1587-1590.

Leahy, D.; Siegel, R.; Klotz, P.; Newman, L. (1975) The separation and characterization of sulfate aerosol. Atmos. Environ. 9: 219-229.

Lee, Y.-H.; Brosset, C. (1978) The slope of Gran's plot: a useful function in the examination of precipitation, the water-soluble part of airborne particles, and lake water. Water Air Soil Pollut. 10: 457-469.

Lee, Y.-H.; Brosset, C. (1979) Interaction of gases with sulphuric acid aerosol in the atmosphere. WMO symposium on the long-range transport of pollutants and its relation to general circulation including stratospheric/tropospheric exchange processes; October; Sofia, Bulgaria. Goeteborg, Sweden: Swedish Water and Air Pollution Research Laboratory; report no. CONF-791065-1. Available from: NTIS; Springfield, VA; IVL-B-504.

Liberti, A.; Possanzini, M.; Vicedomini, M. (1972) The determination of the non-volatile acidity of rain water by a coulometric procedure. Analyst (London) 97: 352-356.

Lindqvist, F. (1985) Determination of ambient sulfuric acid aerosol by gas chromatography/photoionization detection after pre-concentration in a denuder. Atmos. Environ. 19: 1671-1680.

Lioy, P. J.; Daisey, J. M. (1986) Airborne toxic elements and organic substances. Environ. Sci. Technol. 20: 8-14.

Lioy, P. J.; Lippmann, M. (1986) Measurement of exposure to acidic sulfur aerosols. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment and control strategies: proceedings of the second U. S.-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 743-752.

Lioy, P. J.; Waldman, J. (1988) Characteristics and features of ambient concentrations and exposures to acid aerosols. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Lioy, P. J.; Samson, P. J.; Tanner, R. L.; Leaderer, B. P.; Minnich, T.; Lyons, W. (1980) The distribution and transport of sulfate "species" in the New York metropolitan area during the 1977 summer aerosol study. Atmos. Environ. 14: 1391-1407.

Lioy, P. J.; Spektor, D.; Thurston, G.; Citak, K.; Lippmann, M.; Bock, N.; Speizer, F. E.; Hayes, C. (1987) The design considerations for ozone and acid aerosol exposure and health investigations: the Fairview Lake summer camp-photochemical smog case study. Environ. Int. 13: 271-283.

Mack, E. J.; Katz, U. (1976) The characteristics of marine fog occurring off the coast of Nova Scotia. Buffalo, NY: Calspan Corp.; report no. CJ-5756-M-1.

Mack, E. J.; Katz, U.; Rogers, C. W., et al. (1977) An investigation of the meteorology, physics, and chemistry of marine boundary layer processes. Buffalo, NY: Calspan Corp.; report no. CJ-6017-M-1.

Maddalone, R. F.; Shendrikar, A. D.; West, P. W. (1974) Radiochemical evaluation of the separation of H_2SO_4 aerosol by microdiffusion from various filter media. Mikrochim. Acta (Wien): 391-401.

Mader, P. P.; Hamming, W. J.; Bellin, A. (1950) Determination of small amounts of sulfuric acid in the atmosphere. Anal. Chem. 22: 1181-1183.

Morandi, M. T.; Kneip, T. J.; Cobourn, W. G.; Husar, R. B.; Lioy, P. J. (1983) The measurement of H_2SO_4 and other sulfate species at Tuxedo, New York with a thermal analysis flame photometric detector simultaneously collected quartz filter samples. Atmos. Environ. 17: 843-848.

Mrose, H. (1966) Measurements of pH, and chemical analyses of rain-, snow-, and fog-water. Tellus 22: 266-270.

Mueller, P. K.; Hidy, G. M. (1983) The sulfate regional experiment: report of findings. Palo Alto, CA: Electric Power Research Institute; EPRI report no. EA-1901. 3v.

Munger, J. W.; Jacob, D. J.; Waldman, J. W.; Hoffmann, M. R. (1983) Fog water chemistry in an urban atmosphere. J. Geophys. Res. C: Oceans Atmos. 88C: 5109-5121.

National Research Council. (1977) Ammonia. Research Triangle Park, NC: U. S. Environmental Protection Agency, Health Effects Research Laboratory; EPA report no. EPA-600/1-77-054. Available from: NTIS, Springfield, VA; PB-278182/1.

National Research Council. (1983) Acid deposition: atmospheric processes in eastern North America, a review of current scientific understanding. Washington, DC: National Academy Press; pp. 35-40.

Neytzell-de Wilde; Taverner, L. (1958) Experiments relating to the possible production of an oxidizing acid leach liquour by auto oxidation for extraction of uranium. In: Proceedings of the 2nd United Nations international conference on the peaceful uses of atomic energy, v. 3. Geneva, Switzerland.

Okita, T. (1968) Concentration of sulfate and other inorganic metals in fog and cloud water and in aerosol. J. Meteorol. Soc. Jpn. 46: 120-126.

Penzhorn, R.-D.; Filby, W. G. (1976) Eine Methode zur spezifischen Bestimmung von Schwefelhaltigen Saeuren in atmosphaerischen Aerosol [A method for specific determination of sulfur-containing acids in atmospheric aerosols]. Staub Reinhalt. Luft 36: 205-207.

Phillips, M. F.; Gaffney, J. S.; Goodrich, R. W.; Tanner, R. L. (1984) Computer-assisted Gran titration procedure for strong acid determination. Upton, NY: Brookhaven National Laboratory; report no. BNL 35734.

Pierson, W. R.; Hammerle, R. H.; Brachaczek, W. W. (1976) Sulfate formed by interaction of sulfur dioxide with filters and aerosol deposits. Anal. Chem. 48: 1808-1811.

Pierson, W. R.; Brachaczek, W. W.; Korniski, T. J.; Truex, T. J.; Butler, J. W. (1980a) Artifact formation of sulfate, nitrate, and hydrogen ion on backup filter: Allegheny mountain experiment. J. Air Pollut. Control Assoc. 30: 30-34.

Pierson, W. R.; Brachaczek, W. W.; Truex, T. J.; Butler, J. W.; Korniski, T. J. (1980b) Ambient sulfate measurements on Allegheny Mountain and the question of atmospheric sulfate in the northeastern United States. Ann. N. Y. Acad. Sci. 338: 145-173.

Pierson, W. R.; Brachaczek, W. W.; Grose, R. A., Jr.; Japar, S. M.; Norbeck, J. M.; Keeler, G. J. (1987) Atmospheric acidity measurements on Allegheny Mountain and the origin of ambient acidity in the northeastern United States. Atmos. Environ.: submitted.

Rahn, K. A.; Lowenthal, D. (1984) Northeastern and midwestern contributions to pollution aerosol in the northeastern, U.S. Science (Washington, DC) 228: 275-284.

Rahn, K. A.; Borys, R. D.; Butler, E. L.; Duce, R. A. (1979) Gaseous and particulate halogens in the New York City atmosphere. Ann. N. Y. Acad. Sci. 322: 143-151.

Richards, L. W.; Johnson, K. R.; Shepard, L. S. (1978) Sulfate aerosol study. Newbury Park, CA: Rockwell International; report no. AMC8000.13FR.

Richards, L. W.; Mudgett, P. S. (1974) Methods and apparatus for sulfuric acid aerosol analysis. U. S. patent no. 3,833,972.

Rood, M. J.; Larson, T. V.; Covert, D. S.; Ahlquist, N. C. (1985) Measurement of laboratory and ambient aerosols with temperature and humidity controlled nephelometry. Atmos. Environ. 19: 1181-1190.

Samson, P. J. (1980) Trajectory analysis of summertime sulfate concentrations in the northeastern U.S. J. Appl. Meteorol. 19: 1382-1394.

Scaringelli, F. P.; Rehme, K. A. (1969) Determination of atmospheric concentrations of sulfuric acid aerosol by spectrophotometry, coulometry, and flame photometry. Anal. Chem. 41: 707-713.

Scherbatskoy, T.; Klein, R. M. (1983) Response of spruce and birch foliage to leaching by acid mists. J. Environ. Qual. 12: 189-195.

Schlesinger, R. B. (1988) Factors affecting the response of lung clearance systems to acid aerosols: the role of exposure concentration, exposure time, and relative acidity. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Schwartz, S. E. (1984) In: Calvert, J. G., ed. SO_2, NO and NO_2 oxidation mechanisms: atmospheric considerations: v. 3. Boston, MA: Butterworth; pp. 173-208.

Schwartz, S. E.; Newman, L. (1983) Measurements of sulfate production in natural clouds [discussion of Hegg and Hobbs (1982) and reply by authors]. Atmos. Environ. 17: 2629-2633.

Sickles, J. E., II. (1986) Performance and results of the annular denuder system in the sampling and analysis of ambient air near Los Angeles. In: Measurement of toxic air pollutants, proceedings of 1986 EPA/APCA symposium. Pittsburgh, PA: Air Pollution Control Association; APCA publication no. VIP-7; pp. 522-533.

Slanina, J.; van Lamoen-Doornenbal, L.; Lingerak, W. A.; Meilof, W.; Klockow, D.; Niessner, R. (1981) Application of a thermo-denuder analyser to the determination of H_2SO_4, HNO_3 and NH_3 in air. Int. J. Environ. Anal. Chem. 9: 59-70.

Slanina, J.; Schoonebeek, C. A. M.; Klockow, D.; Niessner, R. (1985) Determination of sulfuric acid and ammonium sulfates by means of a computer-controlled thermodenuder system. Anal. Chem. 57: 1955-1960.

Smith-Palmer, T.; Wentzell, B. R. (1986) Ambient acid aerosols in rural Nova Scotia. Water Air Soil Pollut. 30: 837-843.

Spektor, D. M.; Yen, B. M.; Lippman, M. (1988) Effect of concentration and cumulative exposure of inhaled sulfuric acid on tracheobronchial particle clearance in healthy humans. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Spengler, J. D.; Allen, G. A.; Foster, S.; Severance, P.; Ferris, B., Jr. (1986) Sulfuric acid and sulfate aerosol events in two U.S. cities. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P., eds. Aerosols: research, risk assessment and control strategies: proceedings of the 2nd U. S.-Dutch internationalsymposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 107-120.

Spengler, J. D.; Keeler, G. J.; Koutrakis, P.; Raizenne, M. (1988) Exposures to acidic aerosols. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Spicer, C. W. (1986) Patterns of atmospheric nitrates, sulfates and hydrogen chloride in the central Ohio River Valley over a one year period. Environ. Int. 12: 512-518.

Spicer, C. W.; Schumacher, P. M.; Kouyoumjian, J. A.; Joseph, D. W. (1978) Sampling and analytical methodology for atmospheric particulate nitrates: final report. Research Triangle Park, NC: U. S. Environmental Protection Agency, Environmental Sciences Research Laboratory; EPA report no. EPA-600/2-78-067. Available from: NTIS, Springfield, VA; PB-281933.

Spicer, C. W.; Howes, J. W.; Bishop, T. A.; Arnold, L. H.; Stevens, R. K. (1982) Nitric acid measurement methods: an intercomparison. Atmos. Environ. 16: 1487-1500.

Stevens, R. K. (1983) Personal communication.

Stevens, R. K. (1986) Review of methods to measure chemical species that contribute to acid dry deposition. In: Proceedings: methods for acidic deposition measurements. Research Triangle Park, NC: U. S. Environmental Protection Agency; EPA report no. EPA/600/9-88/014.

Stevens, R. K.; Dzubay, T. G.; Russwurm, G.; Rickel, D. (1978) Sampling and analysis of atmospheric sulfates and related species. Atmos. Environ. 12: 55-68.

Stevens, R. K.; Dzubay, T. G.; Shaw, R. W., Jr.; McClenny, W. A.; Lewis, C. W.; Wilson, W. E. (1980) Characterization of the aerosol in the Great Smoky Mountains. Environ. Sci. Technol. 14: 1491-1498.

Tang, I. N.. (1976) Phase transformation and growth of aerosol particles composed of mixed salts. J. Aerosol Sci. 1: 361-371.

Tang, I. N. (1980) Deliquescence properties and particle size change of hygroscopic aerosols. In: Willeke, K., ed. Generation of aerosols and facilities for exposure experiments. Ann Arbor, MI: Ann Arbor Science; pp. 153-167.

Tang, I. N.; Munkelwitz, H. R. (1977) Aerosol growth studies - III. ammonium bisulfate aerosols in a moist atmosphere. J. Aerosol Sci. 8: 321-330.

Tanner, R. L.; Fajer, R. (1981) Upton, NY: Brookhaven National Laboratory; unpublished results.

Tanner, R. L.; Marlow, W. H. (1977) Size discrimination and chemical composition of ambient airborne sulfate particles by diffusion sampling. Atmos. Environ. 11: 1143-1150.

Tanner, R. L.; Cederwall, R.; Garber, R.; Leahy, D.; Marlow, W.; Meyers, R.; Phillips, M.; Newman, L. (1977) Separation and analysis of aerosol sulfate species at ambient concentrations. Atmos. Environ. 11: 955-966.

Tanner, R. L.; Garber, R.; Marlow, W.; Leaderer, B. P.; Leyko, M. A. (1979) Chemical composition of sulfate as a function of particle size in New York summer aerosol. Ann. N. Y. Acad. Sci. 322: 99-113.

Tanner, R. L.; D'Ottavio, T.; Garber, R.; Newman, L. (1980) Determination of ambient aerosol sulfur using a continuous flame photometric detection system. I. Sampling system for aerosol sulfate and sulfuric acid. Atmos. Environ. 14: 121-127.

Tanner, R. L.; Leaderer, B. P.; Spengler, J. D. (1981) Acidity of atmospheric aerosols: a summary of data concerning their chemical nature and amounts of acid. Environ. Sci. Technol. 15: 1150-1153.

Thomas, R. L.; Dharmarajan, V.; Lundquist, G. L.; West, P. W. (1976) Measurement of sulfuric acid aerosol, sulfur trioxide, and the total sulfate content of the ambient air. Anal. Chem. 48: 639-642.

Thurston, G. D.; Lioy, P. J. (1987) Receptor modeling and aerosol transport. Atmos. Environ. 21: 687-698.

Thurston, G. D.; Waldman, J. (1987) Acid aerosol transport episodes in Toronto, Ontario. Presented at: 80th annual meeting of the Air Pollution Control Association; New York, NY. Pittsburgh, PA: Air Pollution Control Association; paper no. 87-89.9.

Tsang, W.; Garvin, D.; Brown, R. C. (1977) NBS kinetic data survey--the formation of nitric acid from hydroxyl and nitrogen dioxide. NBS.

U. S. Environmental Protection Agency. (1982a) Air quality criteria for particulate matter and sulfur oxides. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report nos. EPA-600/8-82-029aF-cF. 3v. Available from: NTIS, Springfield, VA; PB84-156777.

U. S. Environmental Protection Agency. (1982b) Air quality criteria for oxides of nitrogen. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA/600/8-82/026F. Available from: NTIS, Springfield, VA; PB83-163337.

United Kingdom Ministry of Health. (1954) Mortality and morbidity during the London fog of December 1952. London, United Kingdom: Her Majesty's Stationary Office. (Reports on public health and medical subjects no. 95).

Waggoner, A. P.; Weiss, R. E.; Larson, T. V. (1983) In-situ, rapid response measurement of $H_2SO_4/(NH_4)_2SO_4$ aerosols in urban Houston: a comparison with rural Virginia. Atmos. Environ. 17: 1723-1731.

Waldman, J. M.; Hoffmann, M. R. (1987) Pollutant behavior in fog. In: Hites, R. A.; Eisenreich, S. J., eds. Source and fates of aquatic pollutants. Adv. Chem. Ser. (216): 79-129.

Waldman, J. M.; Munger, J. W.; Jacob, D. J.; Hoffmann, M. R. (1985) Tellus 37B: 91-108.

Waldman, J. M.; Lioy, P. J.; Buckley, P.; Thurston, G. (1987) Analyses of spatial patterns in sulfate aerosol acidity within a metropolitan area. In preparation.

Whelpdale, D. M. (1978) Large scale atmospheric sulfur studies in Canada. Atmos. Environ. 12: 661-670.

Wolff, G. T.; Lioy, P. J. (1980) Development of an ozone river associated with synoptic scale episodes in the eastern United States. Environ. Sci. Technol. 14: 1257-1260.

Wolff, G. T.; Kelley, N. A.; Ferman, M. A. (1981) On the sources of summertime haze in the eastern United States. Science (Washington, DC) 211: 703-705.

Wolff, G. T.; Morrissey, M. L.; Kelly, N. A. (1984) An investigation of the sources of summertime haze in the Blue Ridge Mountains using multivariate methods. J. Clim. Appl. Meteorol. 23: 1333-1341.

3. DEPOSITION AND FATE OF INHALED ACID AEROSOLS IN THE RESPIRATORY TRACT

3.1 INTRODUCTION

This chapter first reviews the deposition of inhaled aerosols in the respiratory tract for both humans and experimental animals. The special case of hygroscopic aerosols is then addressed. Finally, an important factor modifying the response to inhaled acids, namely neutralization by airway surface fluid buffers or by endogenous ammonia, is assessed.

The respiratory tract is the major route of exposure to ambient acid aerosols. In order to elicit any response, these aerosols must first deposit on airway surfaces. The deposition of inhaled particles on the internal surfaces of the airways defines the delivery rate to the initial contact site(s) and, for materials that exert their action upon surface contact such as irritants, is a major predicator of response. Deposition is controlled by various physical mechanisms that are influenced by particle characteristics, respiratory airflow patterns and rates, and respiratory tract anatomy. An understanding of deposition is essential for interpretation of the results of the animal toxicologic and human health effects studies discussed later.

Biological effects of aerosols are often related more to the quantitative pattern of deposition within specific respiratory tract regions rather than to total deposition. In regard to particle deposition, three main anatomic regions can be considered: (1) the upper respiratory tract, which includes the airways extending from the nose or mouth through the larynx; (2) the tracheobronchial tree, which includes the conducting airways from the trachea through the terminal bronchioles; and (3) the pulmonary or gas-exchange region, which includes the respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli. Although there are numerous data on regional deposition of particles in humans, many types of exposure protocols require use of experimental animals, with the ultimate goal being extrapolation to humans. To apply results of toxicologic studies adequately in risk assessment, it is essential to consider differences in deposition patterns, since various animal species exposed to the same aerosol may not receive identical doses in comparable sections of the respiratory tract.

3.2 PARTICLE DEPOSITION MECHANISMS AND PATTERNS

The deposition of inhaled particles in the respiratory tract occurs by similar physical mechanisms in humans and experimental animals. There are five significant mechanisms by which deposition may occur: impaction, sedimentation, Brownian diffusion, interception, and electrostatic precipitation.

Impaction is the inertial deposition of a particle onto an airway surface. It occurs when the particle's momentum prevents it from changing course when there is a change in the direction of bulk airflow. Impaction is the main mechanism by which particles having aerodynamic diameters (D_{ae}) $\gtrsim 0.5$ µm deposit in the upper respiratory tract and at or near tracheobronchial tree branching points. The probability of impaction increases with increasing air velocity, rate of breathing, particle density and size.

Sedimentation is deposition due to gravity. When the gravitational force on an airborne particle is balanced by the total of forces due to air buoyancy and air resistance, the particle will fall out of the air stream at a constant rate, known as the terminal settling velocity. The probability of sedimentation is proportional to the particle's residence time in the airway and to particle size and density, and decreases with increasing breathing rate. Sedimentation is an important deposition mechanism for particles with diameters (D_{ae}) $\gtrsim 0.5$ µm that penetrate to those airways where air velocity is relatively low, e.g. mid to small bronchi and bronchioles.

Submicrometer-sized particles, especially those with physical diameters <0.2 µm, acquire a random motion due to their bombardment by surrounding air molecules; this motion may then result in contact with the airway wall. The displacement sustained by the particle is a function of a parameter known as the diffusion coefficient, which is inversely related to particle cross-sectional area. Brownian diffusion is a major deposition mechanism in airways where bulk flow is low or absent, e.g., bronchioles and alveoli. However, extremely small particles may deposit by diffusion in the upper respiratory tract, trachea and larger bronchi.

Interception is a significant deposition mechanism for elongated particles, i.e., fibers, and occurs when the edge of the particle contacts the airway wall. The probability of interception increases as airway diameter decreases, and fibers that are long (e.g., 50 to 100 μm) but thin (e.g., 0.5 μm) can penetrate into distal airways before depositing.

Some freshly generated particles can be electrically charged, and may exhibit enhanced deposition over what would be expected from size alone. This is due to image charges induced on the surface of the airway by these particles and/or to space-charge effects, whereby repulsion of similarly charged particles results in increased migration towards the airway wall. The effect of charge on deposition is inversely proportional to particle size and airflow rate. Since most ambient particles become neutralized naturally due to air ions, electrostatic deposition is generally a minor contributor to overall particle collection by the respiratory tract; it may, however, be important in laboratory studies.

Experimentally determined values for particle deposition within the human respiratory tract as a function of the median size of the inhaled aerosol are presented in the top panels of Figures 3-1 to 3-4. All values are expressed as percentage deposition of the total amount of aerosol inhaled (i.e., deposition efficiency). The obvious variability is due to a number of factors, not the least of which is the use of different experimental protocols in different studies. Figure 3-1 shows the pattern for total respiratory tract deposition. This is characterized by a minimum for particles with diameters of ~0.3 to 0.5 μm. As mentioned, particles with diameters $\gtrsim 0.5$ μm are subject to impaction and sedimentation, while the deposition of those <0.2 μm is diffusion dominated. Particles with diameters between these values are minimally influenced by all three mechanisms, and tend to have relatively prolonged suspension times in air. They undergo minimal deposition after inhalation, and most are, therefore, exhaled.

Studies of deposition in humans generally employ either oral or nasal breathing, and the effect of breathing mode upon deposition is evident from Figure 3-1. Inhalation via the nose results in greater total deposition than does oral inhalation for particles with diameters >0.5 μm; this is due to enhanced collection in the nasal passages. On the other hand, there is little apparent difference in total deposition between nasal or oral breathing for particles with diameters between 0.02 to 0.5 μm.

Figure 3-2 (top) shows the pattern of deposition in the human upper respiratory tract. Again, it is evident that nasal inhalation results in enhanced deposition. The greater the deposition in the head, the less is the

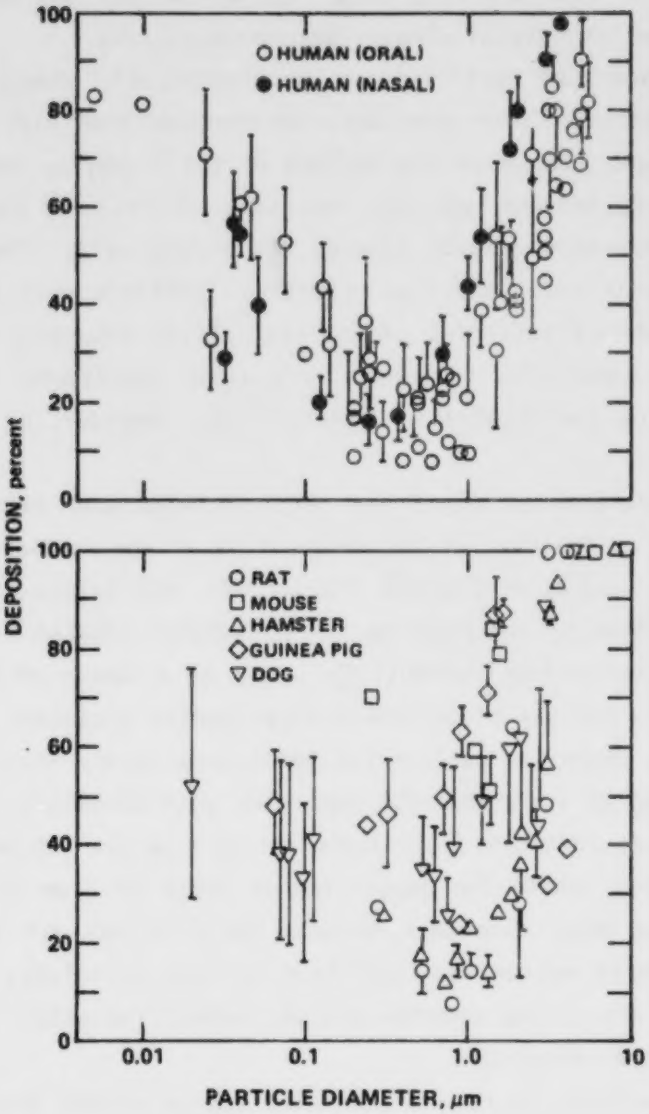


Figure 3-1. Deposition efficiency (percentage deposition of amount inhaled) in humans and experimental animals for total respiratory tract.

Source: Schlesinger (1987).

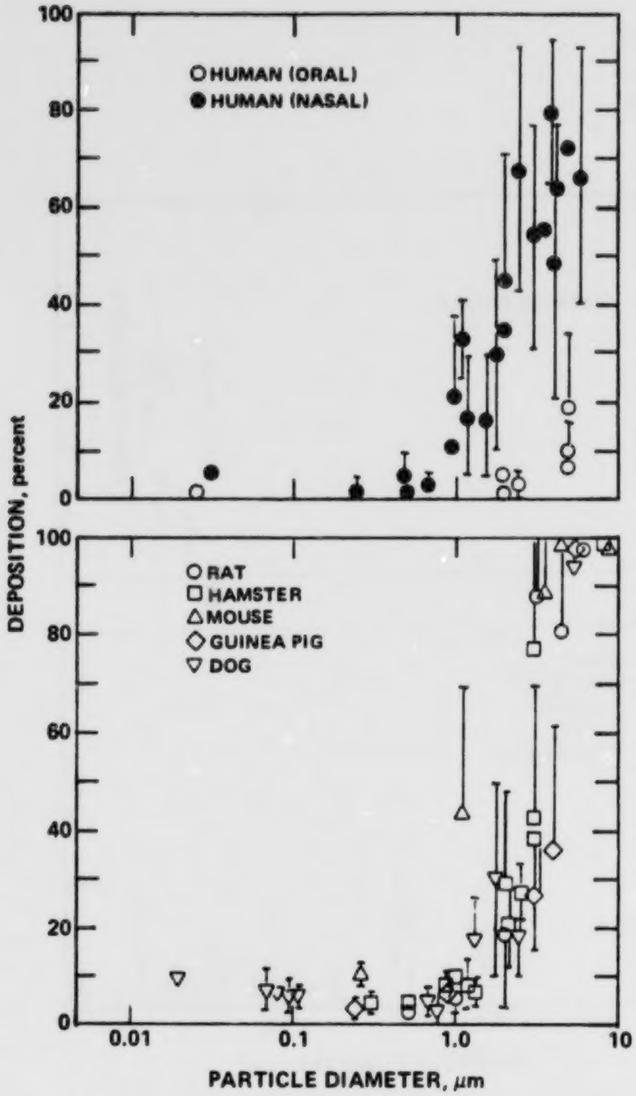


Figure 3-2. Deposition efficiency (percentage deposition of amount inhaled) in humans and experimental animals for upper respiratory tract.

Source: Schlesinger (1987).

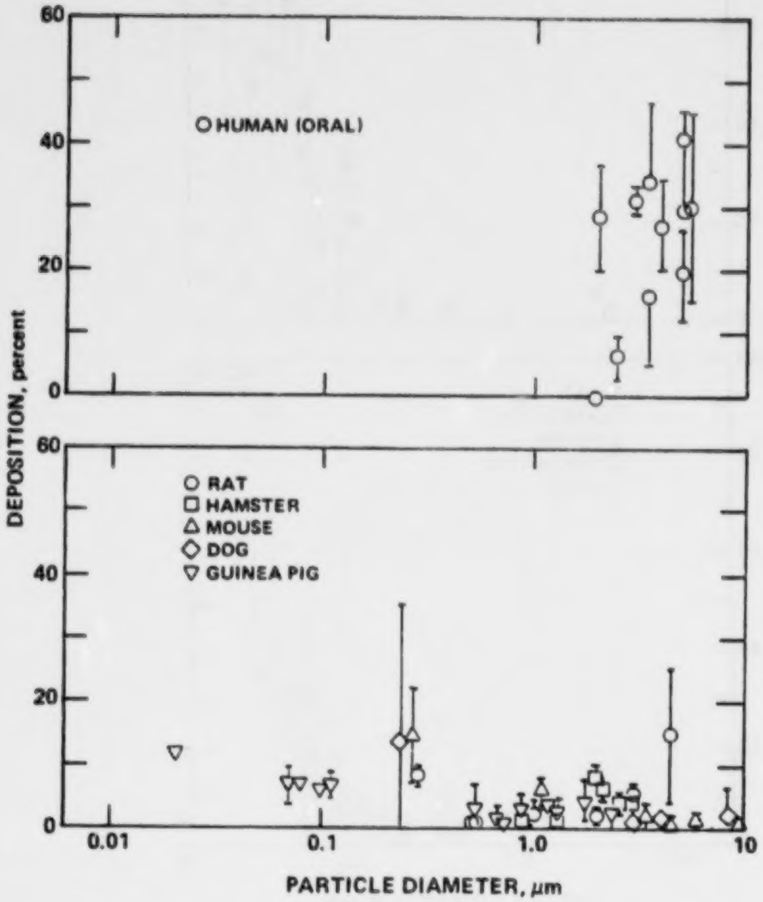


Figure 3-3. Deposition efficiency (percentage deposition of amount inhaled) in humans and experimental animals for tracheobronchial region.

Source: Schlesinger (1987).

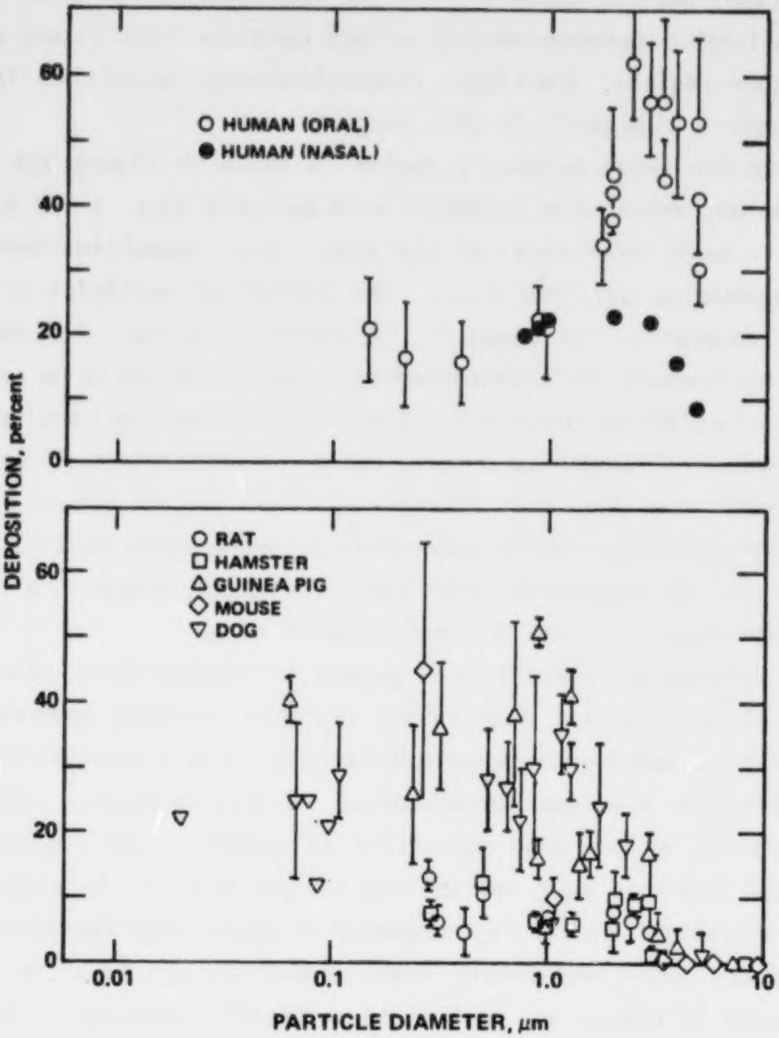


Figure 3-4. Deposition efficiency (percentage deposition of amount inhaled) in humans and experimental animals for pulmonary region.

Source: Schlesinger (1987)

amount available for removal in the lungs. Thus, the extent of collection in the upper respiratory tract affects deposition in more distal regions.

Figure 3-3 (top) depicts deposition in the tracheobronchial tree. In this region, the relationship between deposition and particle size is not as well defined as in other regions; fractional tracheobronchial deposition is relatively constant over a wide particle size range.

Deposition in the human pulmonary region is shown in Figure 3-4 (top). With oral inhalation, deposition increases with particle size, after a minimum at ~0.5 µm. With nasal breathing, on the other hand, deposition tends to decrease with increasing particle size. The removal of particles in more proximal airways determines the shape of the pulmonary curve. For example, increased upper respiratory and tracheobronchial deposition would be associated with a reduction of pulmonary deposition; thus, nasal breathing results in less pulmonary penetration of larger particles, and a lesser fraction of deposition for entering aerosol than does oral inhalation. Thus, in the latter case, the peak for pulmonary deposition shifts upwards to a larger sized particle, and is more pronounced. On the other hand, with nasal breathing, there is a relatively constant pulmonary deposition over a wider range of sizes.

Since much information concerning responses to inhaled acids is collected using experimental animals, the comparative regional particle deposition in these animals must be considered to help interpret, from a dosimetric viewpoint, the implications of animal toxicological results to humans. The bottom panels of figures 3-1 to 3-4 show deposition in commonly used experimental animals. Although there is much variability in the data, it is possible to make some generalizations concerning comparative deposition patterns. The relationship between total respiratory tract deposition and particle size is relatively the same in humans and most of these animals; deposition increases on both sides of a minimum, which occurs for particles of 0.2 to 0.9 µm. Interspecies differences in regional deposition efficiencies occur due to anatomical and physiological factors. In most experimental animal species, deposition in the upper respiratory tract nears 100 percent for particles >2 µm, indicating greater efficiency than that seen in humans. In the tracheobronchial tree, there is a relatively constant, but lower, deposition efficiency for particles of 0.1 to 5.0 µm in all species compared to humans. Finally, in the pulmonary region, deposition efficiency peaks at a lower particle size (~1 µm) in the experimental animals than in humans (2 to 4 µm).

In evaluating studies with aerosols in terms of interspecies extrapolation, it is not adequate to express the amount of deposition merely as a percentage of the total inhaled. Since overall respiratory tract deposition for the same size particle may be quite similar in humans and many experimental animals, it follows that deposition efficiency is independent of body size (McMahon, et al., 1977; Brain and Mensah, 1983). However, different species exposed to identical particles at the same exposure concentration will not receive the same initial mass deposition. If the total amount of deposition is normalized to body weight, smaller animals would receive greater initial particle burdens per unit weight per unit exposure time than would larger ones.

3.3 HYGROSCOPIC AEROSOLS

Most deposition studies tended to focus on insoluble and stable test aerosols whose properties do not change during inhalation. Ambient aerosols, however, usually contain deliquescent or hygroscopic particles that may grow while in transit in the humid respiratory airways. Such particles will deposit according to their hydrated, rather than their initial, size (Blanchard and Willeke, 1984; Cavender et al., 1977). In general, the larger the initial particle size, the less is the absolute growth and growth rate; in any case, the deposition pattern of a specific hygroscopic aerosol can usually be related to its growth characteristics. A comprehensive review of those factors affecting the deposition of hygroscopic aerosols has been provided by Morrow (1986).

Because of dynamic changes in particle size, it is likely that deposition of an acid particle may not be predictable from data on nonhygroscopic aerosols inhaled at the same size. For example, a 1 μm (D_{ae}) particle of H_2SO_4 may grow to nearly 3 μm (D_{ae}) while in the nasal passages, increasing total respiratory tract deposition by a factor of 2 or more over that expected for the original 1 μm particle; this is due to an increase in both upper respiratory tract and tracheobronchial deposition. Concomitantly, there would be a decrease in pulmonary deposition. However, actual differences in deposition may vary, depending upon the initial size of the acid droplet. For example, the relationship between total respiratory tract deposition and inhaled particle size for humans (Figure 3-1) suggests that hygroscopic particles inhaled at <0.5 μm would actually show a decrease in total deposition if they grow no larger than 0.5 μm, and will only begin to show an increase in deposition if the final diameter reached is >1 μm. On the other hand, 0.3 to 0.5 μm hygroscopic particles may show substantial changes in their deposition probability. Particles >5 µm may minimally grow in one respiratory cycle, and may not show an increase in deposition at all compared to similarly sized nonhygroscopic particles (Ferron et al., 1987). Analytical deposition models developed specifically for hygroscopic sulfate particles (Martonen and Patel, 1981a,b) also indicate that total respiratory tract deposition efficiencies for such particles in humans should be greater than those for nonhygroscopic particles if the sulfate originates from particles having diameters larger than 0.1 to 0.3 µm. But even if the total deposition of hygroscopic and nonhygroscopic particles of the same initial size is the same, regional deposition may differ (Martonen et al., 1985).

The deposition of acid sulfate aerosols has been examined in experimental animals. Dahl and Griffith (1983) assessed the deposition of H_2SO_4 aerosols in guinea pigs and rats. Upper respiratory tract and lung, as well as total respiratory tract, deposition of aerosols ranging in size from 0.4 to 1.2 µm (MMAD) was found to increase with increasing initial droplet size. Although the lung deposition of 0.5 µm acid particles was similar to that for 0.5 µm nonhygroscopic particles, 1 µm H_2SO_4 particles deposited much more effectively than did 1 µm nonhygroscopic particles. On the other hand, Dahl et al. (1983) examined the deposition of similarly sized H_2SO_4 aerosols in dogs, and found the deposition pattern at two relative humidities (20 percent and 80 percent) to be similar to that of nonhygroscopic aerosols having the same size. The interindividual variability of deposition in these animals was greater than the differences due to relative humidity. It was suggested that hygroscopicity was not a dominate determinant of deposition site in this larger mammal. Thus, the relative effect of hygroscopicity on ultimate deposition pattern is not resolved, since results using ideal models and those from actual experiments may not agree; in addition, the extent of the effect on deposition may depend upon the animal species.

3.4 NEUTRALIZATION BY AIRWAY SECRETIONS AND ABSORBED AMMONIA

Two important chemical defenses against inhaled acid include endogenous ammonia and airway surface liquid buffers. Acids may react with ammonia to produce ammonium salts or may be buffered by airway secretions. The capacity to buffer or neutralize inhaled acid may thus be an important factor in the eventual toxicity to the organism.

3.4.1 Airway Surface Liquid Buffering

The acid-base equilibrium of airway surface fluids may be altered by buffer content, secretion rate, and presence of inflammation and may differ according to the region of the lung from which the airway secretions are obtained (Lopez-Vidriero et al., 1977). Reported values of sputum pH range from 5 to 8. Changes in pH of airway secretions alter the properties of the mucus macromolecules and hence the viscosity of the mucus gel layer. Secretion of sulfated mucins (sulfomucins) may be partially responsible for alterations in pH.

Gatto (1981) measured the pH of the mucus gel surface layer in rats using a surface pH probe inserted through a tracheal "window." The pH averaged 7.52. Cholinergic stimulation caused a decrease to 7.46, presumably due to increased secretion of acidic glycoproteins and sialic acid in the mucus.

The effect of alterations of pH on ciliary motility and on the morphology of the airway mucosa was examined by Holma et al. (1977). These authors reported that previous studies of cilia from invertebrates, fundamentally similar to human cilia, show that not only the pH but also the ionic composition of the medium influence ciliary motility. Ciliostasis occurs in mammalian respiratory tract cilia at pH's ranging from 5.2 to 6.4. Human bronchial pH was measured with a surface pH electrode inserted via a bronchoscope. This yielded *in situ* measurements of mucus pH (Guerrin et al., 1971). Normal values ranged from 6.5 to 7.5 with a mean of approximately 6.9. These investigators also showed that hypercapnia (respiratory acidosis) was associated with a reduction in mucus pH. Inflammation and infection was associated with considerably more acidic mucus pH's (5.2 to 6.2). Tracheal pH measured in rabbits averaged about 6.6, slightly more acidic than in the humans.

Bodem and co-workers (1983) measured endobronchial pH using a flexible pH probe passed through a bronchoscope and wedging it in a peripheral bronchus. Measurements made in normals and 18 patients revealed a mean pH of 6.6 (range 6.44 to 6.74). The presence of pneumonia in the patients was associated with a slightly lower (6.48) pH. The average endobronchial pH in a group of five dogs was 7.1.

Mucus is converted from a gel to a sol at a pH of about 7.5. Holma et al. (1977) indicate that the mucus is secreted in an alkaline form (and thus as a gel) and is subsequently acidified by carbonic acid formed by CO_2 dissolved in the mucus layer. It was suggested that acidification of the gel layer by inhaled acids or acid forming gases (SO_2, CO_2) would cause increased mucous viscosity and hence increased clearance, provided the pH is not reduced sufficiently to reduce ciliary motility.

Ciliary motility of isolated bovine tracheal strips was studied. Normal ciliary activity was observed in the pH range of 6.7 to 9.7. H_2SO_4 was used for acidification and complete ciliostasis was observed at pH 4.9. Furthermore, at acid pH, epithelial cells "loosened from each other and from the basement membrane". Since normal motility is maintained to pH 6.7 (in cows), Holma et al. (1977) concluded it was unlikely that ambient levels of SO_2 would cause sufficient acidification of the mucus layer to alter ciliary motility. Ciliostasis was typically preceded by intracellular edema.

In a more recent study, Holma (1985) examined the buffer capacity and pH-dependent rheological characteristics of human sputum. The pH of sputum is in equilibrium with respiratory CO_2; the normal sputum pH of about 7.4 is established by the buffering system of the sputum. Sputum equilibrated with 5 percent CO_2 at 37°C and 100 percent RH was titrated with H_2SO_4 to pH 3. Although buffer capacity was variable depending on the sputum sample, depression of sputum pH from 7.25 to 6.5 required the addition of approximately 6 µmol of H^+ per mL of sputum. Sputum from asthmatics had a lower initial pH (6.8; range 6.3 to 7.4) and reduced buffering capacity. Sputum viscosity was minimal at a pH of 7.5 and was increased as the sputum was acidified. Recent work by Holma (Holma, 1988) demonstrates a minimal value for mucus viscosity at a pH of 7.0. Viscosity increased with acidification or alkalinization of the mucus. Since the capacity of mucus to buffer H^+ is reduced in asthmatics, this provides another reason to be concerned with acid aerosol exposure of this sensitive group.

Assuming a tracheobronchial mucus volume of 2.1 mL, between 8 and 16 µmol of H^+ if evenly distributed throughout the airways would be required to depress the pH to 6.5. Since 1 µg H^+ is obtained from 49 µg of H_2SO_4, between 390 and 780 µg of H_2SO_4 would be needed to cause this depression of pH. Assuming exposure duration of 30 min, ventilation of 20 L/min and 50 percent deposition of 100 µg/m^3 H_2SO_4 (1M), 0.6 µmol of H^+ would be deposited in the lung (50 percent x 100 µg/m^3 x (600 L ÷ 1,000 L/m^3) = 30 µg = .3 µmol H_2SO_4 or 0.6 µg of H^+). However, if deposition was localized to airways with a small volume of mucus, less acid would be required to cause reductions in pH.

Fine et al. (1987) hypothesized that buffered acid aerosols (with a greater "hydrogen ion pool") would cause more bronchoconstriction than unbuffered acid aerosols of the same pH. Since the airway surface fluids have a considerable capacity to buffer acid, it was suggested that the buffered acid would cause a more persistent decrease in airway surface pH. If a change in pH is the primary mechanism that triggers bronchoconstriction following inhalation of acid aerosol, then it follows that buffered acids would be more potent bronchoconstrictive agents. The subjects were 8 nonsmoking clinically mild asthmatics whose medications included theophylline and β-sympathomimetic bronchodilators. Their asthma was stable throughout the study and there were no significant deviations in baseline SR_{aw}.

Subjects were first administered unbuffered HCl and H_2SO_4 aerosols of progressively increasing acidity (pH's were 7, 5, 4, 3, 2). The osmolarity of the aerosolized solutions was about 300 mOsm (i.e., isoosmolar). Only one subject experienced a demonstrable increase (120 percent) in SR_{aw} at pH = 2 with HCl; the mean increase was 28 percent for HCl at pH = 2 and 15 percent for H_2SO_4 at pH = 2. With buffered acid aerosols at pH = 2 all subjects (except one with H_2SO_4) experienced at least a 50 percent increase in SR_{aw} (the mean change is not reported since the test was terminated at different levels of titratable acidity for each subject depending on his or her response). Most subjects experienced cough during the acid aerosol challenges.

These studies demonstrate that the acidity of inhaled aerosols is related to their potential to stimulate cough and bronchoconstriction. More specifically, these responses are related to the total available hydrogen ion (titratable acidity), not just the pH. Since airway surface fluids are capable of buffering small amounts of hydrogen ion, the minimal response to unbuffered acids is presumably related to a transient change in airway surface pH. These observations suggest the possibility that persistent effects of acid aerosols (reported in other studies) may be related to persistence of changes in pH of airway surface fluids.

Since most acid fogs are likely to have a low osmolarity, Balmes and colleagues (Balmes et al., 1988a; Balmes et al., 1988b) investigated the hypothesis that increased acidity could potentiate the known effects of hypoosmolar aerosols to cause bronchoconstriction (Sheppard et al., 1983) in subjects with asthma. Subjects were administered increasing quantities of five different aerosols (5.2 to 6.3 μm): hyposmolar saline (HS), HS + H_2SO_4, HS + HNO_3, HS + H_2SO_4 + HNO_3, and issomolar H_2SO_4. All acid solutions were adjusted to pH 2. Response to the aerosols was assessed by giving subjects a series of increasing aerosol concentrations. The amount of aerosol required to increase airway resistance by 100 percent was determined by making a series of SR_{aw} measurements after each dose of aerosol.

The three acid hypoosmolar aerosols caused a 100 percent increase in SR_{aw} at a lower aerosol concentration than did the hypoosmolar saline. There were no differences in responses related to acid composition of the aerosol. Isoomolar H_2SO_4 aerosol did not cause a 100 percent increase in SR_{aw} even at the highest dose, estimated to be 43.5 mg/m^3.

The results of this study support one of the conclusions of Fine et al. (1987), namely that the H^+, not $SO_4^=$ or NO_3^- anion, is the stimulus for bronchoconstriction. However, this study also demonstrates that H^+ is a more potent stimulus to bronchoconstriction when administered as a hypoosmolar aerosol. Nevertheless, as the authors point out, both the water content and the acid content of the aerosols were much higher than would be seen even in the worst case acid fog situation.

Potential risk groups sensitive to acid deposition would include individuals with "acid-saturated" mucus (i.e. low initial pH), individuals whose mucus has a low buffering capacity, or those with an incompletely developed mucociliary system (i.e. infants).

3.4.2 Ammonia Neutralization of Inhaled Acid

Ammonia is present in the expired air of man and animals. Kupprat et al. (1976) reported in man expired volumes of 2 µl at rest and 6 µl during exercise, approximately equivalent to 0.2 ppm or 138 µg/m^3. Robin et al. (1959) reported levels of 0.38 ppm or 262 µg/m^3 in dogs given intravenous NH_4HCO_3 solution.

Larson and co-workers (1977) presented the hypothesis that expired ammonia from the respiratory tract could neutralize a significant portion of inhaled acid aerosol. They used a variety of sampling techniques to determine the source(s) of the respiratory ammonia in a group of 16 subjects. When gas was sampled from the mouth, the median NH_3 concentration ranged from 130 to 210 µg/m^3. Samples taken from the nose or directly from an endotracheal tube had a median concentration of 21 to 29 µg/m^3. It was suggested that the mouth was a major source of expired ammonia, possibly from the bacterial decomposition of salivary urea. One microgram of NH_3 can convert 5.8 µg of H_2SO_4 to ammonium bisulfate or 2.9 µg of sulfuric acid aerosol to ammonium sulfate. It was determined that with the range of respiratory ammonia levels (up to

520 μg/m^3) a maximum of 1,500 μg H_2SO_4 could be neutralized to $(NH_4)_2SO_4$. The extent to which respiratory ammonia can neutralize sulfuric acid aerosol depends not only upon the production of respiratory ammonia but also upon the inspiratory flow rate and the time within the airways that elapses prior to impaction or sedimentation of the aerosol.

Larson et al. (1979a) extended their observations in a group of 10 subjects and observed a higher mean value for ammonia concentration sampled at the mouth of 690 ppb or 475 μg/m^3. These results are comparable to the mean value of 790 ppb (544 μg/m^3) reported by Hunt and Williams (1977). The increase in ammonia levels reported by Larson et al. (1979a) in their second report was apparently due to an improvement in the sampling method.

Larson et al. (1979b) also reported measurements of expired ammonia in the dog. Ammonia concentration at the mouth was 130 μg/m^3 but was only 41 μg/m^3 when measured in the trachea. This again suggested the importance of the oral cavity as a source of ammonia.

Barrow and Steinhagen (1980) found an average expired NH_3 level of 78 ppb in nose-breathing rats, or 54 μg/m^3. This is only slightly higher than results for nose breathing humans, ~25 μg/m^3. Tracheal cannulated rats had NH_3 levels of 286 ppb or about 197 μg/m^3. Thus, these results suggest that the nose is a sink for NH_3 in the rat.

Vollmuth and Schlesinger (1984) measured expired ammonia levels in a group of 5 rabbits. They noted an average expired level of 185 μg/m^3. When the rabbits underwent an oral cleansing and tooth brushing regimen prior to measurement, the NH_3 levels decreased to 126 μg/m^3, indicating a significant oral source of ammonia. Fasting, with oral hygiene, caused a further reduction in expired ammonia to 68 μg/m^3. It was concluded that fasting probably further reduced the oral sources of ammonia and was not associated with reduced amino acid metabolism. Using the model of Larson et al. (1982) it was estimated that about 14 percent of inspired 0.3 μm hygroscopic sulfuric acid aerosol would be neutralized with a NH_3 level of 185 μg/m^3 and an oral cavity residence time of 200 msec.

Larson et al. (1982) measured expired ammonia levels of 31 μg/m^3 (45 ppb) and 57 μg/m^3 (82 ppb) from dogs breathing through the nose or mouth respectively. Ammonia concentration in the trachea averaged 28 μg/m^3 (40 ppb). They calculated the concentration of NH_3 that would be in equilibrium with blood NH_4^+ of 38 μg/m^3.

In addition, NH_3 levels were measured at the trachea for air drawn unidirectional through either the nose or mouth. Similar levels of ~83 $\mu g/m^3$ were seen regardless of whether the air entered via the nose or mouth. Neutralization of inhaled acid aerosol was linearly related to the concentration of NH_3 at the level of the larynx; approximately 60 percent of inhaled 0.5 µm sulfuric acid aerosol was neutralized with laryngeal ammonia levels of ~135 $\mu g/m^3$ and a flow rate of 0.1 L/s. The authors made estimates of neutralization of 100 $\mu g/m^3$ H_2SO_4 in humans using a model based on this study. They estimated that, with oral levels of ammonia, particles less than 0.2 µm would be fully neutralized by ammonia prior to entering the trachea; only about 30 percent of 0.5 µm particles would be neutralized under similar conditions. Larson et al.'s estimates indicate a slightly less efficient neutralization of inhaled acid than the model of Cocks and McElroy (1984).

There appears to be considerable variability in expired ammonia levels from one species to another. The mode of breathing or the location from which ammonia is sampled is also the source of considerable variation. It is important to establish whether these differences are true species differences or methodological differences.

The probability of endogenous ammonia causing neutralization of inspired acid aerosols has been an issue in a number of investigations. Some of the factors implicated in neutralization of acid aerosols have been discussed by Larson et al. (1978). The likelihood of neutralization of acid aerosols depends upon

1. particle size -- small particles are subject to more rapid neutralization than large particles with the same acid concentration
2. concentration of ammonia in the airways
3. concentration of acid in the aerosol - this is partially dependent on hygroscopic growth of the aerosol in the airways
4. residence time of the aerosol in the airways.

It appears that ammonia concentrations are not uniform throughout the respiratory tract, and thus neutralization is also dependent on the avenue of inhalation of acid aerosols; oral inhalation offers the greatest potential for neutralization by ammonia.

Loscutoff et al. (1978) exposed dogs to various levels of sulfuric acid aerosol. With 1 or 3.5 mg/m^3 H_2SO_4, they reported that all expired sulfate was in the form of an ammonium salt. Such measurements, of course, provide no indication of the fate of H_2SO_4 that is deposited within the lung.

Utell et al. (1986) discussed the effects of oral ammonia in a recent symposium presentation. They exposed asthmatics to 350 µg/m^3 sulfuric acid aerosol via mouthpiece under conditions of low (69 µg/m^3) or high (340 µg/m^3) expired ammonia levels. Exposure lasted 10 min while subjects performed light exercise. The reduction in $FEV_{1.0}$ was significantly greater if the subjects were exposed when the oral ammonia levels were lower. The higher oral ammonia level has the potential (i.e., if the reaction goes to completion and uses up all the ammonia) to convert over 900 µg of H_2SO_4 to $(NH_4)_2SO_4$, while the lower ammonia concentration could convert only about 190 µg. These data strongly support the hypothesis that oral or respiratory ammonia may play an important role in the airway toxicity of sulfuric acid aerosol. However, recent studies by Avol et al. (1986) suggest that further investigation of the ammonia neutralization hypothesis is needed.

Cocks and McElroy (1984) have recently presented a model analysis of neutralization of sulfuric acid aerosols in human airways. The acidity of the particles is a function of dilution by particle growth and neutralization by absorbed ammonia. With acid concentrations of 0.14 M, droplet growth does not occur and neutralization is determined principally by ammonia absorption. At higher acid concentrations, droplet growth dilution is a major factor in determination of pH (See Table 3-1).

Table 3-1 presents selected results of the model analysis of Cocks and McElroy (1984). Data are presented for 5.0 (acid fog) and 0.5 µm (acid aerosol) particles at both 500 (oral) and 50 (nasal) µg/m^3 ammonia, at times of 0.1 and 1.0 s, and for two different acid concentrations.

For 0.5 µm particles with H_2SO_4 concentration of 3M, aerosol mass concentration of 100 µg/m^3 and ammonia of 500 µg/m^3, neutralization is complete in 0.3 s. With NH_3 levels of only 50 µg/m^3, neutralization requires 3 s. With an acid concentration of 0.14M, where no particle growth occurs, neutralization proceeds more rapidly. The authors concluded that, even with nasal levels of ammonia, substantial neutralization of droplets less than 0.5 µm would occur. With droplets in the "acid fog" size range and with low pH, neutralization is slowed considerably, especially with low respiratory ammonia levels. However,

TABLE 3-1. MODEL ESTIMATES OF NEUTRALIZATION OF 0.5 AND 5.0 µm PARTICLES BY "ORAL" AND "NASAL" LEVELS OF AMMONIA
(Adapted from Cocks and McElroy, 1984)

H_2SO_4	Aerosol mass µg/m^3	NH_3 µg/m^3	MMAD µm	% Neutralized in	
				0.1s	1.0s
3.3M	1,000	500	5.0	0.6	7.7
		(oral)	0.5	99	99
		50	5.0	0.1	0.8
		(nasal)	0.5	6.9	14.2
	100	500	5.0	0.6	7.9
			0.5	90.2	99.9
		50	5.0	0.06	0.79
			0.5	9.0	81.3
0.14M	1,000	500	5.0	11.7	81.9
			1.0	100	
	100	500	5.0	12	100
			1.0	100	100
		50	5.0	1.2	11.7
			1.0	27	100

the typically dilute solutions in acid fog droplets lend themselves to rapid neutralization such that the reaction of 5 µm particles with oral levels of ammonia would be complete in less than 1.0 s with aerosol mass concentration as high as 100 µg/m^3.

Larson (1988) recently presented a model analysis which considered both airway deposition and ammonia neutralization. This analysis indicates that virtually no acid fog particles will successfully traverse the nasal airway whether ammonia is present or not. During mouth breathing, acid fog particles could reach the larynx and trachea but they are largely neutralized by oral ammonia. Using calculations from this model, the effect of ammonia in decreasing acid deposition of small (and more concentrated) aerosols was much less than for the large particles.

3.5 CONCLUSIONS

The respiratory tract is a target for inhaled particles, as well as a portal of entry by which other organs may be affected. When aerosols are inhaled by humans or experimental animals, different fractions of the inhaled materials deposit by a variety of mechanisms in various locations in the respiratory tract. Particle size distribution and other particle properties, respiratory tract anatomy, and airflow patterns all influence deposition.

Impaction, gravitational settling, and diffusion dominate the deposition of particles in the respiratory tract, with electrostatic attraction and interception being of relatively minor importance. Diffusivity and the interception potential of a particle depend on its geometrical size, whereas the probability of settling and impaction depend on its aerodynamic diameter. Gravitational settling accounts for deposition in the tracheobronchial and pulmonary regions, while impaction contributes to deposition in the upper respiratory tract and tracheobronchial regions. Diffusion primarily affects respiratory tract deposition of particles with diameters smaller than 0.2 μm.

Hygroscopicity is a major particle characteristic which affects deposition. Hygroscopic particles change in size once inhaled, and may have different patterns of deposition when compared to nonhygroscopic particles at the same size; the difference is a function of the initial particle size and composition.

Some portion of inhaled acids will be transformed into the ammonium salts as the acid enters the respiratory tract. Acid that is deposited in the airways prior to reaction with ammonia will be buffered by airway surface fluids. The extent to which these two processes will influence the ultimate fate of the acid will depend upon a number of factors. Larger particles in the "acid fog" size range (5 μm) will be slower to be neutralized but more likely to impact upon the airway walls. Smaller particles (~0.5 μm) are subject to more rapid chemical transformation by ammonia.

The total capacity to buffer or "neutralize" acid is substantial. However, regional capacities vary considerably. For example, the surface liquid buffering capacity of the non-ciliated airways and alveoli is probably quite low. Furthermore, alveolar ammonia levels are lower than in the oral cavity. It is therefore likely that the physiologic effects of inhaled acid aerosols are due to either accumulation of acids at specific sites that overwhelms the neutralization/buffer capacity or to accumulation in lung regions that have a low neutralization/buffer capacity.

3.6 REFERENCES

Avol, E. L.; Linn, W. S.; Hackney, J. D. (1986) Acute respiratory effects of ambient acid fog episodes: final report. NIEHS grant no. ES03291-02; September.

Balmes, J. R.; Fine, J. M.; Gordon, T.; Sheppard, D. (1988a) Potential bronchoconstrictor stimuli in acid fog. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Balmes, J. R.; Fine, J. M.; Christian, D.; Gordon, T.; Sheppard, D. (1988b) Acidity potentiates bronchoconstriction induced by hypoosmolar aerosols. [Manuscript submitted].

Barrow, C. S.; Steinhagen, W. H. (1980) NH_3 concentrations in the expired air of the rat: importance to inhalation toxicology. Toxicol. Appl. Pharmacol. 53: 116-121.

Blanchard, J. D.; Willeke, K. (1984) Total deposition of ultrafine sodium chloride particles in human lungs. J. Appl. Physiol. 57: 1850-1856.

Bodem, C. R.; Lampton, L. M.; Miller, D. P.; Tarka, E. F.; Everett, D. (1983) Endobronchial pH. Am. Rev. Respir. Dis. 127: 39-41.

Brain, J. D.; Mensah, G. A. (1983) Comparative toxicology of the respiratory tract. Am. Rev. Respir. Dis. 128(suppl.): S87-S90.

Cavender, F. L.; Steinhagen, W. H.; McLaurin, D. A., III; Cockrell, B. Y. (1977) Species difference in sulfuric acid mist inhalation. Am. Rev. Respir. Dis. 115(suppl.): 204.

Cocks, A. T.; McElroy, W. J. (1984) Modeling studies of the concurrent growth and neutralization of sulfuric acid aerosols under conditions in the human airways. Environ. Res. 35: 79-96.

Dahl, A. R.; Griffith, W. C. (1983) Deposition of sulfuric acid mist in the respiratory tracts of guinea pigs and rats. J. Toxicol. Environ. Health 12: 371-383.

Dahl, A. R.; Snipes, M. B.; Muggenburg, B. A.; Young, T. C. (1983) Deposition of sulfuric acid mists in the respiratory tract of beagle dogs. J. Toxicol. Environ. Health 11: 141-149.

Ferron, G. A.; Kreyling, W. G.; Haider, B. (1987) Influence of the growth of salt aerosol particles on the deposition in the lung. Ann. Occup. Hyg.: in press.

Fine, J. M.; Gordon, T.; Thompson, J. E.; Sheppard, D. (1987) The role of titratable acidity in acid aerosol-induced bronchoconstriction. Am. Rev. Respir. Dis. 135: 826-830.

Gatto, L. A. (1981) pH of mucus in rat trachea. J. Appl. Physiol. 50: 1224-1226.

Guerrin, F.; Voisin, C.; Macquet, V.; Robin, H.; Lequien, P. (1971) Apport de la pH metric bronchique in situ [Measurement of pH in the bronchi in situ]. In: Ulmer, W. T., ed. Chronic inflammation of the bronchi: proceedings of the Societas Europaea Physiologiae Clinicae Respiratoriae and Gesellschaft fuer Lungen- und Atmungsforschung; December 1969; Bochum, Federal Republic of Germany. Basel, Switzerland: S. Karger; pp. 372-383. (Herzog, H., ed. Progress in respiration research: v. 6).

Holma, B. (1985) Influence of buffer capacity and pH-dependent rheological properties of respiratory mucus on health effects due to acidic pollution. Sci. Total Environ. 41: 101-123.

Holma, B. (1988) Effects of inhaled acids on airway mucus and its consequences for health. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Holma, B.; Lindegren, M.; Andersen, J. M. (1977) pH effects on ciliomotility and morphology of respiratory mucosa. Arch. Environ. Health 32: 216-226.

Hunt, R. D.; Williams, D. T. (1977) Spectroscopic measurements of ammonia in normal human breath. Am. Lab. (Fairfield, Conn.) 9: 10-22.

Kupprat, I.; Johnson, R. E.; Hertig, B. A. (1976) Ammonia: a normal constituent of expired air during rest and exercise. Fed. Proc. Fed. Am. Soc. Exp. Biol. 35: 478.

Larson, T. V. (1988) The influence of chemical and physical forms of ambient air acids on airway doses. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Larson, T. V.; Covert, D. S.; Frank, R.; Charlson, R. J. (1977) Ammonia in the human airways: neutralization of inspired acid sulfate aerosols. Science (Washington, DC) 197: 161-163.

Larson, T. V.; Covert, D. S.; Frank, R. (1978) Respiratory NH_3: a possible defense against inhaled acid sulfate compounds. In: Folinsbee, L. J.; Wagner, J. A.; Borgia, J. F.; Drinkwater, B. L.; Gliner, J. F.; Bedi, J. F., eds. Environmental Stress: individual human adaptations, proceedings of a symposium; August 1977; Santa Barbara, CA. New York, NY: Academic Press; pp. 91-99.

Larson, T. V.; Covert, D. S.; Frank, R. (1979a) A method for continuous measurement of ammonia in respiratory airways. J. Appl. Physiol.: Respir. Environ. Exercise Physiol. 46: 603-607.

Larson, T. V.; Frank, R.; Covert, D. S.; Holub, D.; Morgan, M. (1979b) Measurements of respiratory ammonia and the chemical neutralization of inhaled sulfuric acid aerosol in anesthetized dogs. Am. Rev. Respir. Dis. 119(suppl.): 226.

Larson, T. V.; Frank, R.; Covert, D. S.; Holub, D.; Morgan, M. S. (1982) Measurements of respiratory ammonia and the chemical neutralization of inhaled sulfuric acid aerosol in anaesthetized dogs. Am. Rev. Respir. Dis. 125: 502-506.

Lopez-Vidriero, M. T.; Das, I.; Reid, L. M. (1977) Airway secretion: source, biochemical and rheological properties. In: Brain, J. D.; Proctor, D. F.; Reid, L. M., eds. Respiratory defense mechanisms (in two parts): part I. New York, NY: Marcel Dekker, Inc.; pp. 289, 326.

Loscutoff, S. M.; Burton, F. G.; Killand, B. W. (1978) Neutralization of inhaled sulfuric acid aerosols by ammonia in the lung. Fed. Proc. Fed. Am. Soc. Exp. Biol. 37: 867.

Martonen, T. B.; Patel, M. (1981a) Modeling the dose distribution of H_2SO_4 aerosols in the human tracheobronchial tree. Am. Ind. Hyg. Assoc. J. 42: 453-460.

Martonen, T. B.; Patel, M. (1981b) Computation of ammonium bisulfate aerosol deposition in conducting airways. J. Toxicol. Environ. Health 8: 1001-1014.

Martonen, T. B.; Barnett, A. E.; Miller, F. J. (1985) Ambient sulfate aerosol deposition in man: modeling the infulence of hygroscopicity. EHP Environ. Health Perspect. 63: 11-24.

McMahon, T. A.; Brain, J. D.; Lemott, S. R. (1977) Species differences in aerosol deposition. In: Walton, W. H.; McGovern, B., eds. Inhaled particles IV, part 1: proceedings of an international symposium organized by the British Occupational Hygiene Society; September 1975; Edinburgh, Scotland. Oxford, United Kingdom: Pergamon Press; pp. 23-33.

Morrow, P. E. (1986) Factors determining hygroscopic aerosol deposition in airways. Physiol. Rev. 66: 330-376.

Robin, E. D.; Travis, D. M.; Bromberg, P. A.; Forkner, C. E., Jr.; Tyler, J. M. (1959) Ammonia excretion by mammalian lung. Science (Washington, DC) 129: 270-271.

Schlesinger, R. B. (1987) Biological disposition of airborne particles: basic principles and application to vehicle emissions. In: Air pollution, the automobile and public health. Washington, DC: National Academy Press.: in press.

Sheppard, D.; Rizk, N. W.; Boushey, H. A.; Bethel, R. A. (1983) Mechanism of cough and bronchoconstriction induced by distilled water aerosol. Am. Rev. Respir. Dis. 127: 691-694.

Utell, M. J.; Morrow, P. E.; Bauer, M. A.; Hyde, R. W.; Schrek, R. M. (1986) Modifiers of responses to sulfuric acid aerosols in asthmatics. In: Aerosols: formation and reactivity. London: Pergamon Press.

Vollmuth, T. A.; Schlesinger, R. B. (1984) Measurement of respiratory tract ammonia in the rabbit and implications to sulfuric acid inhalation studies. Fundam. Appl. Toxicol. 4: 455-464.

4. TOXICOLOGICAL STUDIES OF ACID AEROSOLS

4.1 INTRODUCTION

The goal of toxicologic studies is the estimation of risk to humans. Often, this is done empirically with the use of animal models. These serve to identify the nature of responses to toxicant exposure and the range of doses over which such responses occur, and to provide information on mechanisms of potential human toxicity and the pathogenesis of disease. Although studies with experimental animals allow planning of future human studies and are, thus, often done prior to initiating testing with humans, they are also needed for protocols which cannot be used with humans at all, e.g., chronic or repeated exposures which may result in delayed and/or nonreversible changes; such studies serve to assess how the duration, and other conditions, of exposure affect response. In addition, the use of destructive endpoints, such as pathologic assessment, requires animal models even with acute exposure protocols.

This chapter reviews and evaluates the toxicology of acid aerosols in experimental animals. Almost all of the available data have been derived from studies using acid sulfates, i.e., ammonium sulfate ($(NH_4)_2SO_4$), ammonium bisulfate (NH_4HSO_4), and sulfuric acid (H_2SO_4). The bulk of the studies included involve exposure via inhalation; the effects of acids administered by other routes have been discussed only when they help to assess the mechanisms underlying responses to inhaled aerosols.

Although acid aerosols may be constituents of ambient atmospheres, they are usually not the only pollutants present. Thus, the toxicologic effects of pollutant mixtures are of concern in assessing the relative biological significance of ambient acid aerosols. In this section, only studies in which a specific acid is a primary component of the pollutant mix are discussed; those in which the only acid present is formed secondarily due to chemical reaction in the exposure atmosphere have not been included.

It will be evident from this survey of the data base that there is a great deal of variation, both qualitatively and quantitatively, in observed responses to inhaled acids. One major reason involves response differences between species, or between strains of the same species, due to inherent sensitivity differences, or differences in age, health status, aerosol deposition patterns, and respiratory tract NH_3 levels. But even within the same species or strain, variability may be quite large among various studies; this is likely due to the lack of standardization in exposure protocols. A number of experimental variables may impact upon the observed results. Differences in median acid particle size as well as in size distribution affect the extent of aerosol penetration into the respiratory tract, with resultant differences in the mechanism or degree of toxic action at the site of initial contact and, perhaps, the extent of neutralization by respiratory tract NH_3. Hygroscopic growth is also dependent upon the initial size of the acid droplets. Relative humidity of the exposure atmosphere is another important factor affecting the size of the inhaled acid particle and, therefore, the extent and rate of subsequent particle growth. In addition, the nominal acidity of a droplet may be altered by hydration after inhalation, or in the exposure system itself. Other reasons for variability may involve the lack of adequate characterization of the exposure atmosphere at the animal's breathing zone, the failure to validate that the exposure system is dosing the animals as expected, or even differences in the manner in which data are analyzed.

A single major confounding factor in assessing acid aerosol toxicology, and a likely explanation for at least some of the wide variations in response even within one species, is neutralization by both endogenous or exogenous NH_3 (Chapter 3). The former may be affected by factors such as the time between the last feeding and acid exposure and the normal bacterial flora of the respiratory tract, while a major factor influencing exogenous levels is the particular mode of exposure. For example, a greater potential for neutralization exists with whole body chamber exposures, due to the possible release of NH_3 from excrement. In any case, the result of neutralization would be delivery to the animals of less strong acid than anticipated; but without knowing the extent of conversion to less acidic, or neutral, products, the exact composition of the resultant exposure atmosphere is not certain. Thus, in many studies, the actual relation between sulfuric acid levels as measured in the generation or exposure atmosphere and dose to target site is difficult to evaluate. Mode of exposure may also impact upon relative regional deposition and rate of hygroscopic growth. Thus, multiple factors are involved in determining the responses observed in any study, and these factors may interact with each other, accounting for the variations in response to inhaled acid aerosols seen in the current data base.

4.2 MORTALITY

The maximal toxic response is death, and a number of studies have examined the acute lethality of acid aerosols, mainly H_2SO_4. As will be evident with other toxicologic endpoints, large interspecies differences occur. Treon et al. (1950) ranked species in terms of their sensitivity, based upon exposures (chamber) of various duration (15 min to 7 h/d for 5d) to 87 to 1,610 mg/m^3 H_2SO_4 aerosols consisting of particles with diameters mostly <2 µm; the ranking, in order of decreasing sensitivity, was as follows: guinea pig, mouse, rat, rabbit.

Within a particular species of experimental animal, the H_2SO_4 concentration required for lethality may be dependent upon animal age and exposure aerosol particle size. In terms of the former, Amdur et al. (1952) determined the H_2SO_4 (1 µm, MMD) concentration to produce 50 percent mortality (LC_{50}) fcr an 8-hr exposure (chamber) in guinea pigs to be 18 mg/m^3 for 1 to 2 mo old animals, and 50 mg/m^3 for 18 mo old animals. The effect of particle size on lethal concentration is shown in Table 4-1. Although the actual LC_{50} may differ at similar sizes in different studies, the data show that in any one study, smaller particles are less effective than are larger ones.

TABLE 4-1. EFFECT OF H_2SO_4 PARTICLE SIZE ON MORTALITY

Particle Size (µm)	LC_{50}[a] (mg/m^3)	References
0.8 (MMD)	60	Pattle et al. (1956)
2.7 (MMD)	27	Pattle et al. (1956)
0.4 (MMAD)	>109	Wolff et al. (1979)
0.8 (MMAD)	30.3	Wolff et al. (1979)

[a] Based upon 8-hr exposures (chamber) of guinea pigs.

Various environmental factors may confound the response to H_2SO_4. For example, Pattle et al. (1956) noted an increase in H_2SO_4 lethality in guinea pigs when exposure was performed at a cold temperature (0°C), compared to room temperature. This effect was ascribed to the direct action of cold on the constrictive response, i.e., an added stress. On the other hand, temperature differences may also have affected the hydration of the acid particles, which may have altered deposition patterns.

Fairly high concentrations of H_2SO_4 are required for lethality, even in a species as sensitive as the guinea pig. Amdur et al. (1952) found the LC_0 for 8-hr exposures in 1 to 2 mo old guinea pigs to be 8 mg/m^3 (1 µm, MMD). Thomas et al. (1958) found no deaths in guinea pigs exposed (in chambers) continuously (24 hr/d) for 18 to 140 days to 4 mg/m^3 (0.59 to 4.28 µm, MMAD); exposures to 26.5 mg/m^3 (0.59 µm) for 18 to 45 days also resulted in no mortality. Finally, Schwartz et al. (1979) reported an LD_{50} of 100 mg/m^3 H_2SO_4 (0.3 to 0.4 µm, MMAD; σg, ~1.5) for continuous, 7 d exposures (chamber).

The cause of death due to acute, high level H_2SO_4 exposure is laryngeal or bronchial spasm. As the concentration is reduced, more deep pulmonary damage occurs prior to death. Lesions commonly seen are focal atelectasis, hemorrhage, congestion, pulmonary and perivascular edema, and epithelial desquamation of bronchioles; hyperinflation is also often evident (Amdur, 1971; Wolff et al., 1979; Cavender et al., 1977b; Pattle and Cullumbine, 1956). Since death appears to be due largely to an irritant response, differences in the deposition pattern of smaller and larger acid droplets may account for the observed particle size dependence of lethal concentration; larger particles would deposit to a greater extent in the upper bronchial tree, within which the bulk of irritant receptors are located.

A major concern in toxicologic assessment is the relative role of concentration(C) and exposure duration(T) in producing a response. Unfortunately, there are few data available to allow analysis of C x T relationships for acid exposure. Amdur et al. (1952) did examine this in guinea pigs, and found that exposure for 72 h to 8 mg/m^3 H_2SO_4 did not increase mortality percentages over those observed due to 8-h exposures to the same concentration. Thus, lethality appeared to depend on concentration rather than on the duration of exposure. On the other hand, the extent of any histological damage appeared to be related to cumulative exposure (Amdur et al., 1952).

There are few data to allow assessment of relative LC_{50} for acid aerosols other than H_2SO_4. However, Pattle et al. (1956) noted that if sufficient ammonium carbonate was added into the chamber in which guinea pigs were exposed to H_2SO_4 to give excess NH_3, protection was afforded to acid levels that, in the absence of NH_3, would have produced 50 percent mortality. This infers that H_2SO_4 is more acutely toxic than its neutralization products, i.e., NH_4HSO_4 and/or $(NH_4)_2SO_4$. Pepelko et al. (1980) exposed rats (chamber) for 8 h/d for 3 days to $(NH_4)_2SO_4$ at 1,000 to 2,000 mg/m^3 (2 to 3 µm, MMAD); no mortality resulted. On the other hand, 40 percent and 17 percent mortality was observed in guinea pigs exposed once for 8 h to 800 to 900 or 600 to 700 mg/m^3, respectively, of similarly sized-particles; no mortality was observed at levels <600 mg/m^3. Death was ascribed to airway constriction. As with H_2SO_4, guinea pigs are more sensitive to the lethal effects of $(NH_4)_2SO_4$.

The embryotoxic potential of H_2SO_4 has been examined in three species. Hoffman and Campbell (1977) exposed chick embryos continuously, from the 1st through the 14th day of development, to H_2SO_4 at 6.06 mg/m^3 (0.2 to 0.3 µm, MMAD). There was no effect on survival rate nor on organ/body weight ratios, but embryonic weight was slightly, but significantly, reduced, as was serum lactic dehydrogenase activity. This latter was suggested to reflect a delay in normal development. In another study, Murray et al. (1979) exposed pregnant mice and rabbits daily for 7 h, during the major period of organogenesis, to up to 20 mg/m^3 H_2SO_4. There was no evidence of any teratogenic effect, at least based upon histological examination.

4.3 PULMONARY FUNCTION

The earliest studies examining the toxicology of inhaled acid aerosols at sublethal levels used changes in pulmonary function as indices of response. A survey of the data base is presented in Table 4-2.

One of the major exposure parameters that affects response is particle size. In terms of altering pulmonary mechanics, specifically pulmonary resistance in guinea pigs, studies by Amdur (1974) and Amdur et al. (1978a,b) have found the irritant potency of H_2SO_4, $(NH_4)_2SO_4$, or NH_4HSO_4 to increase with decreasing particle size, i.e., the degree of response per unit mass of $SO_4^=$ at any specific exposure concentration increased as particle size decreased, at least within the range of 1 to 0.1 µm. If this is compared to the relationship between particle size and mortality, it is evident that the relative toxicity of different particle sizes also depends upon the exposure concentration; at concentrations above the lethal threshold, large particles are more effective in eliciting response, while at sublethal levels, smaller particles are more effective. There is, however, some indication that even with pulmonary function as the endpoint, a greater response may be obtained with large particles at high concentrations. Thus, Amdur (1958) found that in a series of 1 hr exposures to ~2 to ~40 mg/m^3 H_2SO_4 at sizes of 0.8 or 2.5 µm, the latter size resulted in a greater response only at the highest exposure concentration used.

TABLE 4-2. EFFECTS OF ACID AEROSOLS ON PULMONARY FUNCTION

				Aerosol Characteristics				
Aerosol	Experimental Animal	Exposure[(a)] Technique (Relative Humidity)	Mass Concentration (mg/m^3)	Size (μm)	σg	Exposure Duration	Response[(b)]	Reference
H_2SO_4	guinea pig	head-only (50%)	0.11, 0.4, 0.69, 0.85	1 (MMD)	-	1h	$\uparrow R_L$; $\downarrow C_d$ @ 0.69, 0.85 mg/m^3	Amdur et al. (1978a)
			0.1, 0.51, 1	0.3 (MMD)	-	1h	$\uparrow R_L$; $\downarrow C_d$ nc: V_T, f, MV at any concentration	Amdur et al. (1978a)
H_2SO_4	guinea pig	head-only (38%)	1.9 - 42	0.8 (MMD)	1.32	1h	$\uparrow R_L$, $\downarrow C_d$; $\uparrow V_T$, $\downarrow$f only @42 mg/m^3	Amdur (1958)
			2.3 - 43.6	2.4 (MMD)	1.38	1h	$\uparrow R_L$; $\downarrow C_d$ at > 2.3 mg/m^3; $\downarrow$f @ 43.6 mg/m^3	Amdur (1958)
			30.5	7 (MMD)	2.03	1h	$\uparrow R_L$; nc: C_d, V_T, f	Amdur (1958)
H_2SO_4	guinea pig	head-only (50-55%)	3.02	1.8 (CMD)	1.25	1h		Fairchild et al. (1975a)
			0.32	0.6	1.42	1h	nc: f, V_T, MV	
			0.03	0.25	1.44	1h		
H_2SO_4	guinea pig	chamber (40-80%)	1.2 -48.3	1 (MMAD)	1.3-1.4	1h	$\uparrow R_L$ $\downarrow C_d$ @ $\geq$ 14.6 mg/m^3	Silbaugh et al. (1981b)
H_2SO_4	guinea pig	chamber (50%)	0.08 0.1	0.84 (MMD) 2.78 (MMD	1.5-1.8	52wk (23 h/d) 52wk (23 h/d)	nc: R_L, C_d, DL_{co}, V_T, f, MV, blood gases	Alarie et al. (1973)
H_2SO_4	rat	chamber	2.37	0.5 (MMD)	-	14wk	nc: V_T, f, R_L, C_d, pH, Pa_{co}	Lewkowski et al. (1979)
H_2SO_4	rat	chamber	6.35	0.44 (MMD)	-	6wk	$\downarrow Pa_{co_2}$	Lewkowski et al. (1979)
H_2SO_4	rat	chamber	6.59	0.31 (MMD)	-	13wk	$\uparrow$pH	Lewkowski et al. (1979)
H_2SO_4	dog	endotracheal tube	1, 10	0.1 (CMD)	-	7.5 min	nc: R_r, C_{st}, FRC	Sackner et al. (1978)
	dog	endotracheal tube	5	0.1 (CMD)	-	4h	nc: mechanics, FRC, cardiac output, heart rate	Sackner et al. (1978)

(continued on the following page)

TABLE 4-2. (continued)

Aerosol	Experimental Animal	Exposure Technique[(a)] (Relative Humidity)	Mass Concentration (mg/m^3)	Aerosol Characteristics Size (μm)	Aerosol Characteristics σg	Exposure Duration	Response[(b)]	Reference
H_2SO_4	dog	chamber (43-50%)	0.889	(90% < 0.5, MMAD)		620d (21h/d)	↓DL_{CO}, RV, TLV, heart rate; ↑R_r	Lewis et al. (1973)
H_2SO_4	cynomolgous monkey	chamber (50%)	0.48 2.43	0.54 (MMD) 3.6	1.7-2.2	78wk(22-23 h/d) 78wk(22-23 h/d)	ΔN_2 ↑f; ΔN_2 nc: R_L, C_d	Alarie et al. (1973)
			4.79 0.38	0.73 2.15	1.7-2.2	78wk(22-23 h/d) 78wk(22-23 h/d)	↑f; ΔN_2 ↑f;	
H_2SO_4	donkey	nasopharyngeal catheter (45%)	0.8-1.5 mg/m^3	0.4 (MMAD)	1.5	1h	nc: R_L, C_d	Schlesinger et al. (1978)
H_2SO_4	rabbit	nose-only (50%)	0.25	0.3 (MMAD)	1.6	1h/d, 5d/wk, up to 12 mo.	nc: R_L	Gearhart and Schlesinger (1986)
NH_4HSO_4	guinea pig	head-only (50%)	10.98	0.77 (MMD)	-	1 hr		Amdur et al. (1978b)
			2.6	0.52	-	1 hr	↑R_L; ↓C_d	
			0.93	0.13	-	1 hr		
NH_4HSO_4	dog	endotracheal tube (20-30%)	1	0.1 (CMD)	2.1	7.5 min	nc: R_r, C_{st}, FRC, sG_r, sC, Pa_O, pH	Sackner et al. (1981)
$(NH_4)_2SO_4$	guinea pig	head-only (50%)	9.54	0.8 (MMD)	-	1h		Amdur et al. (1978b)
			2.14	0.2	-	1h		
			1.02	0.3	-	1h	↓C_d; ↑R_L @ 0.5 and 1.02 mg/m^3 only	
			0.5	0.13	-	1h		
$(NH_4)_2SO_4$	guinea pig	chamber (50-60%)	1	0.4 (MMAD)	2.2	6h/d, 5d/wk, 5 or 20d	nc: RV, ↑FRC, VC, TLC, DL_{CO}, C_d, N_2	Loscutoff et al. (1985)

(continued on the following page)

TABLE 4-2. (continued)

Aerosol	Experimental Animal	Exposure[(a)] Technique (Relative Humidity)	Mass Concentration (mg/m³)	Aerosol Characteristics Size (μm)	σ_g	Exposure Duration	Response[(b)]	Reference
$(NH_4)_2SO_4$	rat	chamber (50-60%)	1	0.4 (MMAD)	2.3	6h/d, 5d/wk, 5 or 20d	↑RV;↑FRC; ΔN_2	Loscutoff et al. (1985)
$(NH_4)_2SO_4$	donkey	nasopharyngeal catheter (45%)	0.4 - 2.1	0.4 (MMAD)	1.5	1h	nc: R_L, C_d	Schlesinger et al. (1978)
$(NH_4)_2SO_4$	dog	endotracheal tube (20-30%)	1.1 4.1	0.1 (CMD) 0.2 (CMD)	2.1	7.5 min 4h	nc: R_r, C_{st}, FRC, sG_r, sC, Pa_{O_2}, pH	Sackner et al. (1981)
Na_2SO_4	dog	endotracheal tube (20-30%)	1 5	0.1 (CMD) 0.2 (CMD)	2.1	7.5 min 4h	nc: R_r, C_{st}, FRC, sG_r, sC, Pa_{O_2}, pH	Sackner et al. (1981)
Na_2SO_4	guinea pig	head-only (50%)	0.9	0.11 (MMD)	-	1h	nc: R_L, C_d	Amdur et al. (1978b)
NH_4NO_3	guinea pig	chamber (50-60%)	1	0.6 (MMAD)	2.1-2.3	6h/d, 5d/wk, 5 or 20d	nc: RV, FRC, VC, TLC DL_{CO}, C_d	Loscutoff et al. (1985)
NH_4NO_3	rat	chamber (50-60%)	1	0.6 (MMAD)	2.0	6h/d, 5d/wk, 5 or 20d	↑RV, ↑FRC; ΔN_2	Loscutoff et al. (1985)

(a) Relative humidity refers to the exposure atmosphere. Chamber indicates whole-body exposure.

(b) Key to symbols:
nc: no significant change
↑: significant increase
↓: significant decrease
C_{st}: static compliance
C_d: dynamic compliance
DL_{CO}: diffusing capacity, CO
f: respiratory frequency
FRC: functional residual capacity
MV: minute volume
ΔN_2: change in distribution of ventilation as measured by nitrogen washout technique
Pa_{O_2}: partial pressure of O_2 in arterial blood
Pa_{CO_2}: partial pressure of CO_2 in arterial blood
pH: arterial pH
R_L: pulmonary resistance
R_r: total respiratory resistance
RV: residual volume
sC: specific lung compliance
sG_r: specific respiratory conductance
TLC: total lung capacity
V_T: tidal volume
VC: vital capacity

Pulmonary functional responses to H_2SO_4 suggest a major site of action to be the conducting airways, as evidenced by exposure induced alterations in resistance and compliance. However, some data also suggest that high exposure levels may affect more distal lung regions. Changes in pulmonary diffusing capacity (DL_{CO}), which could indicate damage to the gas-exchange region of the lungs, were noted in dogs exposed at 0.889 mg/m^3 (Lewis et al., 1973); they were not found in guinea pigs exposed at 0.1 mg/m^3 (Alarie et al., 1973). However, deep lung effects of H_2SO_4 are also evident from studies of morphologic and lung defense endpoints, discussed in subsequent sections.

The particle size of the acid aerosol appears to affect the temporal pattern of response. For example, Amdur (1958) observed that changes in pulmonary resistance in guinea pigs following an acute exposure to 0.8 µm H_2SO_4 began immediately, while a delay in the onset of response was observed when 2.5 µm particles were used. In a subsequent study also with guinea pigs (Amdur et al., 1978a), resistance was found to return to control levels by 1/2 hr after exposure to 0.1 mg/m^3 H_2SO_4 when the particle size was 1 µm, but exposure to the same mass concentration of 0.3 µm particles resulted in the maintenance of elevated resistance through this same time. Thus, the response to 0.1 mg/m^3 at 1 µm was slight and rapidly reversible, while that with 0.3 µm droplets was greater and more persistent. At any particular size, however, the degree of change in resistance and compliance in guinea pigs was observed to be dose related, and at exposure concentrations >0.1 mg/m^3 with either 1 or 0.3 µm particles, resistance remained elevated at the 1/2 h post-exposure measurement time.

Although the studies by Amdur and colleagues appear to provide a reasonable picture of the relative effects of acid particle size and exposure concentration on the bronchoconstricive response of guinea pigs at sublethal exposure levels, there is some conflict between these results and reports by others. Whereas the former work supports a concentration dependence for respiratory mechanics alterations, i.e., animals in each exposure group responded uniformly and the degree of response was related to the exposure concentration, others (Wolff et al., 1979; Silbaugh et al., 1981b) have found that individual guinea pigs exposed to H_2SO_4 will show an "all-or-none" constrictive response, i.e., in atmospheres above a threshold concentration, some animals will manifest major changes in pulmonary mechanics ("responders"), while others will not be affected at all ("nonresponders"). As the exposure concentration is increased further, the percentage of the population that is affected, i.e., the ratio of responders to nonresponders, will increase, producing an apparent dose-response relationship. However, the magnitude of the change in pulmonary function is similar for all responders regardless of exposure concentration. Sensitivity to this all-or-none response may be related to an animal's airway caliber prior to H_2SO_4 exposure, since responders had higher pre-exposure values for resistance, and lower values for compliance, than did nonresponders. In any case, the threshold concentration for the all-or-none response is fairly high (>10 mg/m^3 H_2SO_4); in the study of Silbaugh et al. (1981b), deaths of some responders occurred at ≥ 24.3 mg/m^3.

Reasons for the discrepancy with the studies of Amdur and colleagues are not known; they may involve differences in guinea pig strains, ages, health status, or other exposure conditions. In any case, the dyspneic response of the guinea pig responders is similar to asthma attacks in humans, in both its rapidity of onset and in the characteristic obstructive pulmonary function changes with which it is associated.

Another approach to evaluate the acute pulmonary functional response to H_2SO_4 in guinea pigs involves co-inhalation of CO_2 (Wong and Alarie, 1982; Matijak-Schaper et al., 1983; Schaper et al., 1984). This procedure assesses the response to irritants by measuring the decrease in tidal volume (V_T) which is routinely increased above normal by adding 10 percent CO_2 to the exposure atmosphere. Although the exact mechanism underlying a reduction in CO_2 response is not known (e.g., it may be due to changes in resistance or compliance) the assumption is that the change in ventilatory response after irritant exposure is due to direct stimulation of irritant receptors. An exposure concentration dependent decrease in response to CO_2 has been found following 1-hr exposures (head-only) to H_2SO_4 (~1 µm, MMD) at levels ≥ 40.1 mg/m^3 (Wong and Alarie, 1982). Subsequently, Schaper et al. (1984) exposed guinea pigs (head-only) for 0.5 h to H_2SO_4 at 1.8 to 54.9 mg/m^3 (0.6 µm, AED, $\sigma g = 2.9$). At concentrations >10 mg/m^3, the level of response (i.e., the maximum decrease in ventilatory response to CO_2) increased as a function of exposure concentration. However, below 10 mg/m^3, there was no relation between exposure concentration and response; in these cases, the effect was transient, with a decrease in CO_2 response occurring at the onset of acid exposure, but subsequently fading.

The results of the studies with CO_2 differ from those of both Silbaugh et al. (1981b) and Amdur and colleagues, in that there was neither an "all or none" response as seen by the former, nor was a concentration-response relationship observed at H_2SO_4 concentrations <10 mg/m^3 as reported by the latter. In addition, Amdur and colleagues observed sustained changes in lung function, rather than a fading response, at low concentrations. The reasons for these differences are unknown, but may partly reflect inherent sensitivity differences of the experimental techniques and/or animal strains used.

The relative potency of various sulfates to alter resistance or compliance in guinea pigs with acute exposure was examined by Amdur et al. (1978b). They found that the percentage increase in resistance per unit mass of $SO_4^=$ (at equivalent particle sizes) was greater for H_2SO_4 than for either $(NH_4)_2SO_4$ or NH_4HSO_4. However, NH_4HSO_4 was found to be less potent than was $(NH_4)_2SO_4$. The greater irritancy of $(NH_4)_2SO_4$ compared to NH_4HSO_4 is unexpected, since the former is less acidic. This particular ranking was not found in pulmonary function studies in humans (Utell et al., 1982) nor in mucociliary transport studies in rabbits (Schlesinger, 1984). Using an acidic NO_x salt, i.e., NH_4NO_3, Loscutoff et al. (1985) found no changes in pulmonary mechanics in rats or guinea pigs exposed to 1 mg/m^3 (0.6 µm) for 6 h/d, 5 d/wk for up to 20 d; $(NH_4)_2SO_4$ was more potent in this regard.

The specific mechanism underlying acid induced pulmonary functional changes is not known, but irritant receptor stimulation may occur due to direct contact by deposited particles or due to humoral mediators released as a result of exposure. In terms of the latter, a possible candidate in mediation of the bronchoconstrictive response, at least in guinea pigs, is histamine. Charles and Menzel (1975) incubated guinea pig lung fragments with various salts, including $(NH_4)_2SO_4$, NH_4NO_3, NH_4Cl, NaCl, and Na_2SO_4. The first three resulted in histamine release in proportion to their concentration ($(NH_4)_2SO_4$ was the most effective), while no histamine release was found with the latter two. Since $SO_4^=$ itself appeared not to be involved in the response (no effect was seen with Na_2SO_4) and NH_4^+ was apparently needed for sulfate-mediated histamine release, this mechanism would not seem to explain the bronchoconstrictive effects due to H_2SO_4 exposure. However, in whole animal studies, similar pulmonary function responses were found in guinea pigs exposed to histamine or H_2SO_4 (Popa et al., 1974; Silbaugh et al., 1981b), and H_2SO_4 exposure resulted in degranulation of mast cells (Cavender et al., 1977a). Whether histamine is involved in other species of animals is not certain. Interspecies differences in response to histamine do exist; perhaps this is one factor accounting for interspecies response differences to H_2SO_4.

Evidence for a direct response to H_2SO_4 in altering pulmonary function is found using the CO_2 coinhalation procedure. Schaper and Alarie (1985) noted that the responses to histamine and H_2SO_4 differed in both their magnitude and temporal relationship, suggesting direct action of the inhaled acid.

There are few data to allow an interspecies comparison of acid aerosol induced pulmonary function response, but examination of the available evidence (Table 4-2) suggests that guinea pigs are more sensitive than the other species examined. An exception is the study by Loscutoff et al. (1985), in which rats were more affected by exposure to $(NH_4)_2SO_4$ than were guinea pigs; this was not supported by the $(NH_4)_2SO_4$ mortality study of Pepelko et al. (1980). The reason for this discrepancy is unknown.

The results of pulmonary function studies indicate that H_2SO_4 is a bronchoactive agent that will alter lung mechanics of exposed animals primarily by constriction of smooth muscle; however, the threshold concentration for this response is quite variable, depending upon the animal species and measurement procedure used. But although changes in resistance and compliance are markers of exposure, the health significance of these in normal individuals is unknown. On the other hand, all subgroups of an exposed population may not have equal sensitivity to inhaled pollutants. In fact, some may be especially sensitive. For example, in humans increased hospital admissions in summer for acute respiratory disease, including asthmatic attacks, may be related to ozone, sulfate and temperature (Bates and Sizto, 1986). These investigators speculate that the O_3 and sulfate may be surrogates for other pollutants; it has been suggested that one possibility for the latter is H_2SO_4 (Lippmann, 1985). Some lung diseases, the most notable of which is asthma, involve a change in airway "responsiveness", i.e., an alteration in the degree of reaction to exogenous (or endogenous) bronchoactive agents, resulting in increased airway resistance at levels of these agents which do not affect normal individuals. Such altered airways are called hyperresponsive. The use of pharmacologic agents capable of inducing smooth muscle contraction, a technique known as bronchoprovocation challenge testing, can assess the state of airway responsiveness after exposure to a nonspecific stimulus such as an inhaled irritant.

The ability of H_2SO_4 aerosols to alter airway responsiveness has been assessed in two studies. Silbaugh et al. (1981a) exposed guinea pigs (chamber, 80 percent RH) for 1 hr to 4 to 40 mg/m^3 H_2SO_4 (1.01 µm, MMAD, $\sigma g = 1.3-1.7$) and examined the subsequent response to inhaled histamine. Some of the animals showed an increase in pulmonary resistance and a decrease in compliance at H_2SO_4 concentrations ≥ 19 mg/m^3 and without histamine challenge; only the animals showing this constrictive response during acid exposure also had major increases in histamine sensitivity, suggesting that airway constriction may have been a prerequisite for the development of hyperresponsivity. In another study, Gearhart and Schlesinger (1986) exposed rabbits (nose-only, 80 percent RH) to 0.25 mg/m^3 H_2SO_4 (0.3 µm, MMAD; $\sigma g = 1.6$) for 1 h/d, 5 d/wk, and assessed airway responsiveness after 4, 8, and 12 mo of exposure, using acetylcholine administered intravenously. Hyperresponsivity was evident at 4 mo, and a further increase was found by 8 mo; the response at 12 mo was similar to that at 8 mo, indicating a stabilization of effect. Unlike the previous results in guinea pigs, there was no change in baseline resistance (i.e., measured prior to bronchoprovocation challenge) at any time during the acid exposures. Thus, repeated exposures to H_2SO_4 resulted in the production of hyperresponsive airways in previously normal animals; this may then "sensitize" the airways to further acid exposure, or to exposure to other airborne materials.

The mechanism that underlies sulfuric acid-induced airway hyperresponsiveness is not clear. Neither is its relation to airway disease. Although hyperresponsivity is associated with specific diseases, its pathogenetic significance is not understood. Human asthmatics and, to some extent, chronic bronchitics typically have hyperresponsive airways (Ramsdell et al., 1982; Ramsdale et al., 1985; Simonsson, 1965), but it is not known whether this state is a predisposing factor in clinical disease, or merely a reflection of other changes in the airways that precede it. At this point, circumstantial evidence supports the hypothesis that an increase in airway responsivity may be a risk factor in development of obstructive airway disease (Fish and Menkes, 1984). More work is clearly needed to resolve this issue.

From the previous discussion, it is possible that one particular group of individuals that may have altered response to pollutants are those with respiratory disease. Unfortunately, there are very few data to allow examination of the effects of different disease states in experimental animals upon response to acid aerosols. Rats and guinea pigs with elastase-induced pulmonary emphysema were examined to assess whether repeated exposures (6 h/d, 5 d/wk, 20 d) to $(NH_4)_2SO_4$ (1 mg/m^3, 0.4 µm MMAD) or NH_4NO_3 (1 mg/m^3, 0.6 µm MMAD) would alter pulmonary function compared to saline-treated controls (Loscutoff et al., 1985). Similarly, dogs having lungs impaired by exposure to NO_2 were treated with H_2SO_4 (0.889 mg/m^3, 21 h/d, 620 d) (Lewis et al., 1973). Both of these studies indicated that the specific disease states induced did not enhance the effect of acid aerosols in altering pulmonary function; in some cases, there were actually fewer functional changes in the diseased lungs than in the unimpaired animals. It is, however, possible that other types of disease states could result in enhanced response to inhaled acid aerosols; as mentioned, asthma is a likely one.

4.4 RESPIRATORY TRACT MORPHOLOGY AND BIOCHEMISTRY

Morphologic damage associated with exposure to lethal levels of acid aerosols has been previously discussed. Of greater concern, perhaps, are those changes associated with sublethal exposures. A survey of these, as determined microscopically, is provided in Table 4-3.

Single or multiple exposures to H_2SO_4 at fairly high levels ($\gg 1$ mg/m^3) is associated with a number of characteristic responses, e.g., alveolitis, bronchial and/or bronchiolar epithelial desquamation, and edema. However, the sensitivity of morphologic endpoints to these exposure levels is dependent upon the animal species. Comparative sensitivity of the rat, mouse, rhesus monkey and guinea pig was examined by Schwartz et al. (1977) using mass concentrations of H_2SO_4 ≥ 30 mg/m^3 at comparable particle sizes. Both the rat and the monkey were quite resistant, while the guinea pig and mouse were the more sensitive species. The nature of lesions in the latter two were similar, but differed in location; this is, perhaps, a reflection of differences in the deposition pattern of the acid droplets. Mice would tend to have greater deposition in the upper respiratory airways than would rats (Schlesinger, 1985), which could account for the laryngeal and upper tracheal location of the lesions seen in the former. The relative sensitivity of the guinea pig and relative resistance of the rat to acid sulfates is supported by results from other morphological studies (Busch et al., 1984; Cavender et al., 1977b; Wolff et al., 1986).

As mentioned previously, the severity of lung histologic damage appears to depend upon total dose, rather than concentration alone. For example, guinea

TABLE 4-3. EFFECTS OF ACID AEROSOLS ON RESPIRATORY TRACT MORPHOLOGY

Aerosol	Experimental Animal	Exposure Technique (Relative Humidity)	Mass Concentration (mg/m³)	Aerosol Characteristics Size (μm)	Aerosol Characteristics σg	Exposure Duration	Response	Reference
H_2SO_4	guinea pig	chamber (70-90%)	32.6	1 (MMAD)	1.49	4h	diffuse pulmonary hyperinflation; focal atelectasis; epithelial desquamation in terminal bronchioles	Brownstein (1980)
H_2SO_4	guinea pig	chamber (40-45%)	8	1 (MMAD)	-	8 - 72h	thickening of alveolar wall; atelectasis; congestion in alveoli and bronchi	Amdur et al. (1952)
H_2SO_4	guinea pig	chamber	25	---	-	1 - 6h	regional alveolitis develops during 3rd and 4th hr of exposure; necrosis of alveolar capillary endothelium	Cavender et al. (1977a)
H_2SO_4	guinea pig	chamber (80%)	1.2, 9, 27	0.8 - 1 (MMAD)	1.5-1.6	6h	at 27 mg/m³: focal hyperinflation with distended alveoli, interstitial edema only in "responders"; no change in "nonresponders" or at 1 and 10 mg/m³. Concentration dependent increase in height of tracheal mucus layer at all concentrations	Wolff et al. (1986)
H_2SO_4	guinea pig	chamber (55%)	10 30 100	0.89 (MMD) 0.83 0.72	-	5d 5d 5d	no effect at 10 mg/m³; mortality at 30 and 100 mg/m³	Cavender et al. (1977b)
H_2SO_4	guinea pig	-	2 - 8	---	-	5d	edema; cellular infiltration around bronchi and blood vessels	Bushtueva (1957)
H_2SO_4	guinea pig	chamber (55%)	20	0.53, 0.99, 1.66 (MMD)	-	7 - 28d	diffuse, regional alveolitis; focal hemorrhage; infiltration of mononuclear cells into alveolar lumen; edema	Cavender et al. (1977b)
H_2SO_4	guinea pig	chamber (55-60%)	25	1 (MMD)	1.6	6h/d, 2d	alveolar hemorrhage and interstitial edema; desquamation of bronchiolar epithelium; proliferation of Type II cells; vesiculation of capillary endothelium; increase in macrophage no. in alveoli; no lesions in bronchi, trachea, larynx	Cockrell et al. (1978)

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TABLE 4-3. (continued)

Aerosol	Experimental Animal	Exposure Technique (Relative Humidity)	Mass Concentration (mg/m³)	Aerosol Characteristics Size (μm)	Aerosol Characteristics σg	Exposure Duration	Response	Reference
H_2SO_4	guinea pig	chamber (≤60%)	30 38 71	0.31 (MMAD) 0.31 (MMAD) 0.52 (CMD)	1.6 1.6 -	7d 7d 4d	71 mg/m³: focal edema, necrosis of alveolar septa, inflammatory cell infiltration; necrosis of bronchiolar epithelium; focal epithelial necrosis in larger bronchi; ciliary denudation. 38 mg/m³: minimal effects; some change in density and length of cilia	Schwartz et al. (1977)
H_2SO_4	guinea pig	chamber (63%)	10	0.83 (AED)	1.7	6h/d, 5d/w, 6 mo.	some proliferation of alveolar macrophages; some cilia loss in trachea	Cavender et al. (1978)
H_2SO_4	guinea pig	chamber	1.15 - 26.5	0.59, 0.93 4.28 (MMAD)	-	continuous up to 5 mo.	epithelial desquamation in bronchi primarily, with 0.9 μm	Thomas et al. (1958)
H_2SO_4	guinea pig	chamber	0.9	0.49 (MMD)	1.6-4.3	52wk(22-23 h/d)	no effect	Alarie et al. (1975)
H_2SO_4	guinea pig	chamber (50%)	0.1 0.08	2.38 (MMD) 0.84	1.5-1.8	52wk(22-23 h/d) 52wk	no effect no effect	Alarie et al. (1973)
H_2SO_4	mouse	chamber (≤60%)	140 170	0.32 (MMAD) 0.62 (MMAD)	1.4 1.7	14d 10d	lesions in larynx and upper trachea; epithelial ulceration, edema, inflammatory infiltration	Schwartz et al. (1977)
H_2SO_4	rat	chamber	1 - 100	0.6-1.1 (MMAD)	1.7-1.8	6h	100 mg/m³: some cilia loss; ulceration of larynx. <100: no effect	Henderson et al. (1980a)
H_2SO_4	rat	chamber (80%)	1.1, 11, 96	0.8 - 1 (MMAD)	1.6-1.8	6h	laceration of larynx and cilia loss in bronchi @ 96 mg/m³; no deep lung lesions; some thickening of mucus lining in trachea at 11 and 96 mg/m³	Wolff et al. (1986)
H_2SO_4	rat	chamber (55%)	10 30 100	0.89 (MMD) 0.83 0.72	-	5d 5d 5d	no effect	Cavender et al. (1977b)

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TABLE 4-3. (continued)

Aerosol	Experimental Animal	Exposure Technique (Relative Humidity)	Mass Concentration (mg/m^3)	Aerosol Characteristics		Exposure Duration	Response	Reference
				Size (µm)	σg			
H_2SO_4	rat	chamber (40-60%)	2	0.3 (MMD)	~2	8h/d, 82d	some hypertrophy of epithelial cells, mainly at alveolar duct level; no effect on turnover rate of terminal bronchiolar epithelial or Type II cells	Juhos et al. (1978)
H_2SO_4	rat	chamber (63%)	10	0.83 (AED)	1.7	6h/d 5d/w, 6 mo.	no effect	Cavender et al. (1978)
H_2SO_4	rat	chamber (50%)	0.7-1.2	0.03-0.04 (CMD)	1.8-2.1	continuous, up to 180d	no effect	Moore and Schwartz (1981)
H_2SO_4	rat	chamber (≤60%)	45 68 172	0.52 (CMD) 0.4 (MMAD) 0.45 (CMD)	- - -	11d 6d 7d	no effect in nasal passages, trachea, bronchi, alveolar region	Schwartz et al. (1977)
H_2SO_4	dog	chamber (43-50%)	0.889	90% < 0.5 (MMAD)	-	21h/d, 620d	some interstitial inflammation, but no overall clearcut changes	Lewis et al. (1973)
H_2SO_4	cynomolgous monkey	chamber (50%)	0.38	2.15 (MMD)		78wk (23 h/d)	bronchiolar epithelial hyperplasia	Alarie et al. (1973)
			2.43	3.6	1.7-2.2	78wk (23 h/d)	bronchiolar epithelial hyperplasia; thickening of alveolar septa	Alarie et al. (1973)
			0.48	0.54		78wk (23 h/d)	no effect	Alarie et al. (1973)
			4.79	0.73		78wk (23 h/d)	hyperplasia in bronchioles and mid-bronchi	Alarie et al. (1973)
H_2SO_4	rhesus monkey	chamber (≤60%)	150	0.3 - 0.5 (CMD)	-	3d		Schwartz et al. (1977)
			361	0.43 (MMAD)	1.6	7d	no effect	
			502	0.48 (MMAD)	1.5	7d		

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TABLE 4-3. (continued)

Aerosol	Experimental Animal	Exposure Technique (Relative Humidity)	Mass Concentration (mg/m³)	Aerosol Characteristics Size (µm)	Aerosol Characteristics σg	Exposure Duration	Response	Reference
H_2SO_4	rabbit	oral tube or nose-only (80%)	0.25 - 0.5	0.3 (MMAD)	1.6	1h/d, 5d/wk, 4wk	increased epithelial thickness in small airways; increase in secretory cells in mid to small airways	Schlesinger et al. (1983)
H_2SO_4	rabbit	nose-only (80%)	0.25	0.3 (MMAD)	1.6	1h/d, 5d/wk up to 52wk	increase in secretory cell density throughout bronchial tree increased in number of small airways	Gearhart and Schlesinger (1987)
$(NH_4)_2SO_4$	guinea pig	chamber	1.03	0.42 (MMD)	2.25	6h/d, 5d/wk, 20d	interstitial thickening; hypertrophy and hyperplasia of Type II cells and secretory cells in bronchioli	Busch et al. (1984)
$(NH_4)_2SO_4$	rat	chamber	5	0.8 - 1 (MMD)	1.8-2.0	7d	no effect (proximal acinar region)	Last et al. (1983)
$(NH_4)_2SO_4$	hamster	chamber	0.187	0.3 (MMD)	2.02	6h/d, 5d/wk, 15wk	emphysematic lesions; no hyperplasia of bronchial glands or metaplasia of goblet cells	Godleski et al. (1984)
$(NH_4)_2SO_4$	rat	chamber	300	1 - 2 (MMAD)	-	8h/d, 1 - 14d	no effect	Pepelko et al. (1980)
$(NH_4)_2SO_4$	rat	chamber	1.03	0.42 (MMAD)	2.25	6h/d, 5d/wk, 20d	interstitial thickening	Busch et al. (1984)
NH_4NO_3	rat guinea pig	chamber	1	0.6 (MMAD)	2.2	6h/d, 5d/wk, 4wk	no effect (alveolar region)	Busch et al. (1986)

pigs exposed to 8 mg/m^3 H_2SO_4 for 72 hr (C x T = 576 (mg/m^3)·h showed more extensive tissue damage than did those exposed at 20 mg/m^3 for 8 h (C x T = 160 (mg/m^3)·h. There was no mortality at the first condition, but 50 percent at the second (Amdur et al., 1952).

With mortality and pulmonary mechanics as endpoints, the particle size of the acid droplet plays a role in relative toxicity. There are conflicting data in this regard with morphologic alteration, although the reasons for this are unclear. Thomas et al. (1958) exposed guinea pigs for 5 mo to >1 mg/m^3 H_2SO_4 at three sizes, 0.59, 0.93, and 4.28 µm (MMAD). At nonlethal levels, the midsize particle appeared to be the most effective in producing a morphologic response. More recently, however, Cavender et al. (1977b) exposed guinea pigs to 20 mg/m^3 H_2SO_4 for 7 to 28 d at three particle sizes, 0.53, 0.99, and 1.66 µm (MMD). There was no apparent size-related difference in response. Similarly, Alarie et al. (1975) noted no size dependence (<1 µm to 5 µm) for the histopathologic effect of >1 mg/m^3 H_2SO_4 exposures in monkeys.

Repeated or chronic exposures to H_2SO_4 at concentrations ≤ 1 mg/m^3 produce a response characterized by hypertrophy and hyperplasia of epithelial secretory cells. In morphometric studies of rabbits exposed to 0.25 to 0.5 mg/m^3 H_2SO_4 (0.3 µm) for 1 h/d, increases in the relative number or density of secretory cells have been found to extend to the bronchiolar level (Schlesinger et al., 1983; Gearhart and Schlesinger, 1988), where these cells are normally rare or absent. The changes began within 4 wk of exposures, and persisted for up to 3 months following the end of exposure. Persistently increased secretory cell number in peripheral airways is significant, since an excess of mucus in this region, a likely consequence of this increase (Jeffery and Reid, 1977), is associated with chronic bronchitis (Hogg et al., 1968; Matsuba and Thurlbeck, 1973).

A shift in the relative number of smaller airways in rabbits was found after 4 mo of exposure to 0.25 mg/m^3 (0.3 µm) for 1 hr/d, 5 d/wk (Gearhart and Schlesinger, 1988). Changes in airway size distribution due to irritant exposure, specifically cigarette smoke, has been reported in humans (Petty et al., 1983; Cosio et al., 1978); in these cases, the size change is ascribed to inflammation. It is, therefore, of interest that the response seen in the acid-exposed rabbits was not accompanied by inflammation. In any event, size change seems to be an early change relevant to clinical small airways disease.

Damage to the respiratory tract following exposure to acid aerosols may be determined by methods other than direct microscopic observation. Analysis of bronchopulmonary lavage fluid obtained from exposed animals can also provide valuable information. For example, levels of cytoplasmic enzymes, such as lactic dehydrogenase (LDH) and glucose-6-phosphate dehydrogenase (G-6PD), are markers of cytotoxicity; an increase in lavageable protein suggests increased permeability of the alveolocapillary barrier; levels of membrane enzymes, such as alkaline phosphatase, are markers of disrupted membranes; the presence of fibrin degradation products (FDP) provide evidence of general damage; and sialic acid, a component of mucoglycoprotein, may be an indicator of mucus secretory activity. A lack of alteration in lavage indices suggests that there was no major injury to the lungs.

Henderson et al. (1980b) exposed rats (chamber) for 6 h to H_2SO_4 (0.7 µm, MMAD) at 1.5, 9.5, and 98.2 mg/m^3 and found FDP in blood serum after exposure at all concentrations. No FDP was found in the lavage fluid, but since the washing procedure did not include the upper respiratory tract (i.e., anterior to and including the larynx), the investigators concluded that the FDP observed in the serum was an indicator of upper airway injury. An exposure concentration dependent increase in sialic acid content of the lavage fluid was also observed; this was ascribed to increased secretory activity in the tracheobronchial tree.

Wolff et al. (1986) exposed both rats and guinea pigs for 6 h to H_2SO_4 (0.8 to 1 µm, MMAD), at levels of 1.1 to 96 mg/m^3 for the former and 1.2 to 27 mg/m^3 for the latter. No changes in LDH, lavageable protein nor sialic acid content of lavage fluid was found in the rat. However, some of the guinea pigs exhibited bronchoconstriction after exposure to 27 mg/m^3, and only these animals showed increased levels of lavageable protein, sialic acid and LDH. No change in lavageable protein was found in the lungs of rats exposed for 3 d (23.5 h/d) to 1 mg/m^3 (0.4 to 0.5 µm, MMAD) H_2SO_4 (Warren and Last, 1987), nor for 2 d (23.5 h/d) to 5 mg/m^3 (0.5 µm, MMAD) $(NH_4)_2SO_4$ (Warren et al., 1986).

The hydroxyproline content of the lungs may provide an index of collagen deposition or degradation. No change in total lung synthesis or content of hydroxyproline was found in rat lungs after exposure for 7 d (23.5 h/d) to 4.84 mg/m^3 (0.5 µm, MMAD) $(NH_4)_2SO_4$, nor due to a 7 d exposure to 1 mg/m^3 (0.5 µm) H_2SO_4 (Last et al., 1986).

A series of studies by Last and colleagues assessed the synthesis of collagen by minces prepared from rat lungs after *in vivo* acid sulfate exposure; this is a possible indicator of the potential for pollutants to produce fibrosis. Exposure for 7 d (23.5 h/d) to H_2SO_4 at 0.04, 0.1, 0.5, and

1 mg/m^3 (0.4 to 0.5 µm, MMAD) resulted in no increase in collagen synthesis rate (Warren and Last, 1987). No effect on collagen synthesis by rat lung minces was found due to 7 d exposures to $(NH_4)_2SO_4$ at 5 mg/m^3 (0.8 to 1 µm, MMAD) (Last et al., 1983).

Another parameter of damage and/or inflammation is change in lung DNA, RNA or total lung protein. No significant changes in any of these were found in rats after exposure to 1 mg/m^3 H_2SO_4 (<1 µm) for 3 d (Last and Cross, 1978), nor in tissue protein content in rats exposed for up to 9 d to a similar concentration of H_2SO_4 (Warren and Last, 1987).

The data base concerning morphological alterations shows that acid sulfates are both upper airway and deep lung irritants. But the specific pathogenesis of acid-induced lesions is not known. As with pulmonary mechanics, both a direct irritant effect of deposited acid droplets on the epithelium and/or indirect effects, perhaps mediated by humoral factors such as histamine, may be involved. Similar lesions have been produced in guinea pig lungs by exposure to either histamine or H_2SO_4 (Cavender et al., 1977a); however, the former appears to initiate the lesions, and once they are so initiated, further acid exposure produces necrosis more rapidly than does further histamine exposure. In addition, some lesions may be secondary to reflex bronchoconstriction, to which guinea pigs are very vulnerable, rather than primary effects separable from constriction. Thus, damage at the small bronchi and bronchiolar level may be due not only to direct acid droplet-induced injury, but to indirect reflex-mediated injury (Brownstein, 1980).

The mechanism underlying secretory cell hyperplasia at low H_2SO_4 exposure levels is also unknown; it may involve an acid-induced increase in division of existing cells, or transition from a different cell type. Other irritants (e.g., tobacco smoke and SO_2) have been shown to result in the conversion of one epithelial cell type into another, e.g., serous cell to goblet cell, or Clara cell to goblet cell (Reid et al., 1983; Phipps, 1981; Reid and Jones, 1979).

4.5 RESPIRATORY TRACT DEFENSES

The response to air pollutants often depend upon interaction with an array of nonspecific and specific respiratory tract defenses. The former consist of nonselective mechanisms protecting against a wide variety of inhaled materials; the latter require immunologic stimulation for activation. Although these systems may function independently, they are linked; for example, response to an immunologic insult may enhance subsequent response to non-antigenic materials as well. The overall efficiency of lung defenses determines the local residence times for inhaled deposited material, which has a major influence upon the degree of pulmonary response; furthermore, depression or over-activity of these systems may be involved in the pathogenesis of lung disease.

Studies of altered lung defenses due to inhaled acid aerosols have concentrated on examination of conducting and respiratory region clearance function; there are only a few studies of effects upon immunologic competence.

4.5.1 Clearance Function

Clearance, a major nonspecific defense mechanism, is the physical removal of material that deposits on airway surfaces. The mechanisms involved are regionally distinct. In the conducting (i.e., tracheobronchial) airways, clearance occurs via the mucociliary system, whereby a mucus "blanket" overlying the ciliated epithelium is moved by the coordinated beating of the cilia towards the oropharynx. The mucus cover is actually bilayered, at least in the central airways. It consists of a lower hypophase (sol) overlying the epithelium and bathing the cilia, and an upper epiphase (gel) resting on top of the cilia.

In the respiratory (i.e., alveolated) region of the lungs, clearance occurs via a number of mechanisms and pathways, but the major one for both microbes and nonviable particles is the alveolar macrophage. These cells rest freely within the fluid lining of the alveolar epithelium where they move by ameboid motion. Via phagocytic ingestion of deposited particles, macrophages help prevent penetration through the alveolar epithelium and subsequent translocation to other sites. These cells contain proteolytic enzymes, allowing digestion of a wide variety of organic materials, and they also kill bacteria through peroxide-producing oxidative mechanisms. In addition, macrophages are involved in the induction and expression of immune reactions. Thus, the macrophage provides a link between the lung's nonspecific and specific defense systems. Macrophages may be cleared from the respiratory region along a number of pathways, but the primary one is via the mucociliary system after these cells reach the distal terminus of the mucus blanket (Bowden, 1984).

4.5.1.1 Conducting Airways - Mucociliary Clearance. The assessment of effects upon mucociliary clearance due to inhaled acid aerosols often involved examination solely of mucus transport rates in the trachea, since this is a readily accessible airway and tracheal mucociliary clearance measurements are more straightforward to perform than are those aimed at assessing clearance from the entire tracheobronchial tree. Table 4-4 outlines reported studies of acid aerosol effects upon tracheal mucociliary clearance; all of the available data are for sulfate compounds.

Although many of the studies involved fairly high concentrations of acid aerosols, most demonstrated a lack of effect. The most likely explanation for this is that the size of the aerosol used precluded significant tracheal deposition. This is supported by noting that Wolff et al. (1981) found tracheal transport rates in dogs to be depressed only when using 0.9 µm H_2SO_4, while no effect was seen with a 0.3 µm aerosol at an equivalent mass concentration. In any case, the use of tracheal clearance rate as a sole toxicologic endpoint may be misleading, inasmuch as other studies (Schlesinger et al., 1978, 1979) have demonstrated changes in bronchial clearance that were not associated with any change in tracheal transport.

The results of studies assessing the effects of acid aerosols upon bronchial mucociliary clearance are outlined in Table 4-5. Observed responses to H_2SO_4 indicate that the direction of clearance change, i.e., slowing or speeding, following acute exposure is dependent upon both exposure concentration (C) and exposure time (T) (Schlesinger, 1988); stimulation of clearance occurs at low CxT values, and retardation at higher levels. However, the actual value needed to produce an observed acceleration may be dependent upon the region within the bronchial tree from which clearance is being measured, in relation to the region that is most affected by the deposited acid (Leikauf et al., 1984). Thus, in effect, low H_2SO_4 exposure concentrations, i.e., ~0.1 to 0.3 mg/m^3 for 1 hr, accelerate clearance from the large proximal airways, where little deposit, while slowing clearance from the distal ciliated airways, where there is greater acid deposition. At higher exposure concentrations, i.e., > ~0.75 mg/m^3 for 1 hr, mucociliary clearance from both proximal and distal conducting airways is depressed.

Comparison of responses to H_2SO_4 suggest that there are possible interspecies differences in sensitivity of mucociliary clearance to inhaled acid aerosols (Wolff et al., 1986). As an example, the speeding of tracheal transport in the rat with ~100 mg/m^3 H_2SO_4 seems anomalous since, in other species,

TABLE 4-4. EFFECTS OF ACID AEROSOLS ON TRACHEAL CLEARANCE

Aerosol	Experimental Animal	Exposure Technique (Relative Humidity)	Mass Concentration (mg/m³)	Aerosol Characteristics Size (μm)	Aerosol Characteristics σg	Exposure Duration	Response[(a)]	Reference
H_2SO_4	sheep	head-only	14	0.1 (CMD)	-	0.3h	nc	Sackner et al. (1978)
			4	0.1 (CMD)	-	4h	nc	Sackner et al. (1978)
H_2SO_4	dog	nose-only (80%)	1	0.3 (MMAD)	1.2	1h	nc	Wolff et al. (1981)
			5	0.3 (MMAD)	1.2	1h	nc	Wolff et al. (1981)
H_2SO_4	dog	nose-only	1	0.9 (MMAD)	1.3	1h	↓	Wolff et al. (1981)
H_2SO_4	dog	nose-only	0.5	0.9 (MMAD)	1.3	1h	↓	Wolff et al. (1981)
H_2SO_4	donkey	nasophoryngeal catheter (45%)	0.2 - 1.4	0.4 (MMAD)	1.5	1h	nc	Schlesinger et al. (1978)
H_2SO_4	rat	chamber (82%)	1 - 100	0.6 - 0.8 (MMAD)	1.5-2.6	6h	↑	Wolff et al. (1980)
H_2SO_4	rat	nose-only (80%)	10 - 100	0.4 - 0.6 (MMAD)	1.3-1.4	0.5h	↑	Wolff et al. (1980)
H_2SO_4	rat	chamber (80%)	1.1, 11, 96	0.9 - 1 (MMAD)	1.6-1.8	6h	↑ @ 96 mg/m³	Wolff et al. (1986)
H_2SO_4	guinea pig	chamber (80%)	1.4, 9, 27	0.8 - 0.9 (MMAD)	1.5-1.6	6h	↓ @ 1.4 mg/m³	Wolff et al. (1986)
NH_4HSO_4	sheep	head-only (20-30%)	1	0.1 (CMD)	2.1	4h	nc	Sackner et al. (1981)
$(NH_4)_2SO_4$	donkey	nasopharyngeal catheter (45%)	0.3 - 3.0	0.4 (MMAD)	1.5	1h	nc	Schlesinger et al. (1978)
$(NH_4)_2SO_4$	sheep	head-only (20-30%)	1.1	0.1 (CMD)	2.1	4h	nc	Sackner et al. (1981)

(a) Key to symbols:

nc: = no significant change
↑: = significant acceleration of clearance
↓: = significant slowing of clearance

TABLE 4-5. EFFECTS OF ACID AEROSOLS ON BRONCHIAL CLEARANCE

Aerosol	Experimental Animal	Exposure Technique (Relative Humidity)	Mass Concentration (mg/m^3)	Aerosol Characteristics		Exposure Duration	Response[(a)]	Reference
				Size (µm)	σ_g			
H_2SO_4	rabbit	oral tube (75%)	0.1 - 2.2	0.3 (MMAD)	1.6	1h	↑, ↓ (depending on concentration and duration)	Chen and Schlesinger (1983); Schlesinger et al. (1984); Schlesinger (1988)
H_2SO_4	rabbit	oral tube or nose-only (80%)	0.25 - 0.5	0.3 (MMAD)	1.6	1h/d, 5d/wk, 4wk	↑; persistent	Schlesinger et al. (1983)
H_2SO_4	rabbit	nose-only (80%)	0.25	0.3 (MMAD)	1.6	1h/d, 5d/wk, 12 mo.	↓ by 1 week; progressive slowing after 19wk; persistent	Gearhart and Schlesinger (1988)
H_2SO_4	donkey	nasopharyngeal catheter (45%)	0.2 - 1.4	0.4 (MMAD)	1.5	1h	↓; persistent in 2 of 4 animals	Schlesinger et al. (1978)
H_2SO_4	donkey	nasopharyngeal catheter (45%)	0.1	0.5 (MMAD)	1.5	1h/d, 5d/wk, 6 mo.	↓; persistent in 2 of 4 animals	Schlesinger et al. (1979)
H_2SO_4	mouse	chamber (70%)	1.5	0.6 (CMD)	~2.2	4h	nc	Fairchild et al. (1975b)
			15	3.2 (CMD)	~1.5	4h	↓	Fairchild et al. (1975b)
H_2SO_4	rat	nose-only(39%;85%)	3.6	1.0 (MMAD)	1.9-2.3	4h	nc	Phalen et al. (1980)
NH_4HSO_4	rabbit	oral tube (78%)	0.6 - 1.7	0.4 (MMAD)	1.6	1h	↓ @ 1.7 mg/m^3	Schlesinger (1984)
$(NH_4)_2SO_4$	rabbit	oral tube (78%)	2	0.4 (MMAD)	1.6	1h	nc	Schlesinger (1984)
$(NH_4)_2SO_4$	donkey	nasopharyngeal catheter (45%)	0.3 - 3.0	0.4 (MMAD)	1.5	1h	nc	Schlesinger et al. (1978)
$(NH_4)_2SO_4$	rat	nose-only(39%;85%)	3.6	0.4 (MMAD)	1.9-2.3	4h	nc	Phalen et al. (1980)

(a) Key to symbols:

nc: = no significant change
↑: = significant acceleration of clearance
↓: = significant slowing of clearance

levels $\geq$1 mg/m^3 produce mucociliary depression. The reasons for this observation are not known. The rat is less susceptible to the lethal effects of H_2SO_4, and it does not have strong bronchoconstrictive reflex responses following H_2SO_4 exposures. These characteristics, together with the lack of effect of H_2SO_4 on bronchial clearance at fairly high exposure levels (3.6 mg/m^3 for 4 hr), suggest that the mucociliary system of the rat may also differ in sensitivity from most of the other species studied. Although the lack of response of tracheal transport in the guinea pig at H_2SO_4 levels >1 mg/m^3 is also surprising, its response at 1 mg/m^3 is also different from that of the rat and more in line with other species (Wolff, 1986). As with all studies, however, it should be borne in mind that differences in experimental variables, such as aerosol particle size, may contribute to some extent to apparent response differences between species.

The relative irritant potency of acid sulfate aerosols, in terms of altering mucociliary clearance, is likely related to their degree of acidity. Schlesinger (1984) exposed rabbits for 1 h to submicrometer aerosols of NH_4HSO_4, $(NH_4)_2SO_4$ and Na_2SO_4. Exposure to ~0.6 to 1.7 mg/m^3 NH_4HSO_4 produced a significant depression of clearance rate only at the highest level. No significant effects were observed with the other sulfate compounds at levels up to ~2 mg/m^3. When these results are compared to those from a study using H_2SO_4 (Schlesinger et al., 1984), the ranking of irritant potency is found to be $H_2SO_4 > NH_4HSO_4 > (NH_4)_2SO_4$, Na_2SO_4; this strongly suggests a relation between the hydrogen ion (H^+) concentration (total acidity) and the extent of bronchial mucociliary clearance alteration. In another study, Schlesinger et al. (1978) found bronchial clearance to be altered in donkeys exposed to H_2SO_4 for 1 hr at levels above ~0.2 mg/m^3, while exposures to $(NH_4)_2SO_4$ at up to 3 mg/m^3 produced no response.

The mechanism by which deposited acid aerosol may alter clearance is not certain. The effective functioning of mucociliary transport depends upon optimal beating of the cilia and the presence of mucus having appropriate physicochemical properties. Both ciliary beating and mucus viscosity may be affected by the deposition of acid (Holma, 1985). Normally, tracheobronchial mucus has a pH of ~6.5 to 8.2 (Kwart et al., 1963; Guerrin et al., 1971; Gatto, 1981; Holma et al., 1977). In vitro studies have shown that, at alkaline pH, mucus is more fluid than at acid pH; the inflection point occurs at a pH between 7.5 to 7.6 (Breuninger, 1964). A small increase in viscosity which may occur due to deposited acid could "stiffen" the mucus blanket, perhaps promoting the clearance mechanism and, thus, increasing its efficiency (Holma et al., 1977). Such a scenario may occur at low H_2SO_4 exposure concentrations, where ciliary activity would not be directly affected by the acid, and is consistent with clearance acceleration observed at these concentrations with acute exposure. However, the exact relation between mucus viscosity and transport rate is not certain; differential alterations in rheological properties of the sol or gel layers may have different effects upon the system (Puchelle and Zahm, 1984).

Higher exposure concentrations of H_2SO_4, in addition to altering mucus viscosity, may also affect ciliary beating. Schiff et al. (1979) and Grose et al. (1980) found that 2- to 3-h in vivo exposures of hamsters to ~0.9 to 1 mg/m^3 H_2SO_4 resulted in a depression of ciliary beating frequency in tracheal explants prepared after exposure. In vitro studies indicate that complete ciliostasis will occur if the pH is low enough (Holma et al., 1977); however, regional ciliostasis, presumably with a change in clearance function, may occur at pH values above this critical level. Thus, a H^+-induced depression of ciliary beating, due to a direct impact upon the cilia and/or to a change in mucus viscosity, could account for the observed retardation of clearance observed at high concentrations of H_2SO_4 (or NH_4HSO_4) with acute exposures.

There is some evidence, however, that the response to H_2SO_4 may not be entirely due to the free H^+. Schiff et al. (1979) exposed hamster tracheal rings in vitro to H_2SO_4 in medium for 3 h and examined ciliary beat frequency and cytology; the pH of the medium was ~5. There was no effect upon beat frequency when the tissue was examined within 1 h after exposure, although morphological damage was evident at this time; at 24 h after exposure, beat frequency was depressed. They then exposed tracheal explants for 3 h to the same medium as above, but with the pH adjusted to 5 using hydrochloric acid (HCl). Exposure under this condition resulted in a reduction in beat frequency, but no change in cell morphology. When these latter explants were transferred to fresh culture medium, the cilia resumed beating at their normal frequency. According to the investigators, these results indicated that medium at pH 5 itself produced no lasting morphological effects, and that acidity alone (at least as measured by pH) was not responsible for the observed morphological and functional effects produced by the H_2SO_4. Fine et al. (1987) have suggested that response is due to total H^+ concentration rather than pH.

Another (or an additional) mechanism by which deposited acid may affect mucociliary clearance is via alteration in the rate and/or amount of mucus secretion. A mild, irritant induced increase in the quantity of mucus, to which the mucociliary system adapts by speeding transport, is consistent with the initial increase in bronchial clearance rates observed following acute exposures to low concentrations of H_2SO_4. Direct evidence for hypersecretion is limited. In a study that examined secretory rate, Last and Cross (1978) showed that exposure of rats for 23.5 h/d for 3 days to submicrometer H_2SO_4 at ~1 mg/m^3 did not affect the secretion of mucus glycoprotein from tracheal explants prepared after exposure; however, the effect on secretion from smaller conducting airways was not examined. On other hand, Henderson et al. (1978), using analysis of lavage fluid to detect responses in the lungs of rats exposed to 1, 10, or 100 mg/m^3 H_2SO_4 for 6 h, showed a dose related increase in sialic acid content, which the authors suggested to indicate increased mucus secretion. Although mild irritation may increase clearance rate, at some point, oversecretion due to higher exposure concentrations will likely result in an overloading of the clearance system, and a retardation in transport rate (Wolff, 1986; Albert et al., 1973). This likely occurs with repeated or chronic exposures, even to lower (0.1-0.25 mg/m^3) acid concentrations.

The airways actively transport ions, and the interaction between transepithelial ion transport and consequent fluid movement is important in the maintenance of the mucus lining. A change in ion transport due to deposited acid particles may, for example, alter the depth and/or composition of the sol layer (Nathanson and Nadel, 1984), perhaps affecting clearance rate. Although no data are available regarding acid sulfates, Stutts et al. (1981) found that ammonium nitrate (NH_4NO_3) altered sodium and chloride transport across canine tracheal epithelium. The response was ascribed to NH_4^+ rather than to NO_3^-, since sodium nitrate ($NaNO_3$) had no effect; mucociliary transport was not examined.

The pathological significance of transient alterations in bronchial clearance rates in healthy individuals is not certain, but such changes are an indication of a lung defense response. On the other hand, persistent impairment of clearance may lead to the inception or progression of acute or chronic respiratory disease and, as such, may be a plausible link between inhaled acid aerosols and respiratory pathology.

Short-term exposures to acid aerosols may lead to persistent clearance changes. Schlesinger et al. (1978) demonstrated that weekly 1-h exposures of donkeys to submicrometer H_2SO_4 at 0.2 to 1 mg/m^3 produced a transient slowing of bronchial clearance in 3 of 4 animals. However, two of the four (including one that did not respond after any individual test) developed persistently slowed clearance after about 6 of the exposures; this slowing persisted for two months after all acid exposures had ceased.

The development of persistent alterations after a relatively small number of 1-h weekly exposures emphasizes that, in order to evaluate fully the impact ambient acid aerosols might have upon the inception and progression of respiratory disease, it is essential to consider the effects of intermittent exposures, especially at low exposure concentrations. Thus, as a follow-up to the above study, Schlesinger et al. (1979) exposed the two donkeys that had shown only transient responses, as well as two previously unexposed animals, to 0.1 mg/m^3 H_2SO_4 for 1 h/d, 5 d/week for 6 months. Within the first few weeks of exposure, all four animals developed erratic clearance rates. The two previously unexposed animals developed persistently slowed bronchial clearance during the second three months of exposure, and during four months of follow-up clearance measurements, while the two previously exposed animals adapted to the new exposures in the sense that their clearance times fell consistently within the normal range during the last few months of acid exposure. However, after the end of the exposure series, their clearance rates were significantly faster than prior to any acid exposures, and remained so for the entire follow-up period (Lippmann et al., 1982).

Schlesinger et al. (1983) exposed rabbits to 0.25 to 0.5 mg/m^3 H_2SO_4 (0.3 µm, MMAD) for 1 h/d, 5 d/wk for 4 weeks, during which time bronchial mucociliary clearance was monitored. Clearance was accelerated on specific individual days during the course of the acid exposures, especially at 0.5 mg/m^3. In addition, clearance was significantly faster, compared to preexposure levels, during a 2-week follow-up period after acid exposures had ceased.

The longest-term exposure at relatively low H_2SO_4 levels for examination of effects on bronchial clearance was the study of Gearhart and Schlesinger (1988). Rabbits were exposed to 0.25 mg/m^3 H_2SO_4 for 1 h/d, 5 d/wk for up to 52 wk, and some animals were also provided a three month follow-up period. Clearance was slower during the first month of exposure and this slowing was maintained, and became progressive, throughout the rest of the exposure period. After cessation of exposure, clearance became still slower (a phenomenon seen in the donkey study, above), and did not return to normal by the end of the follow-up period. No significant change in clearance was observed in sham control animals. Differences in the direction of clearance change between this study and that of Schlesinger et al. (1983) were due to differences in exposure protocol. In both studies, however, histologic analysis indicated the development of increased numbers of epithelial secretory cells, especially in small airways, the likely consequence of which would be an increase in mucus production. In addition, the slowing of clearance seen by Gearhart and Schlesinger (1988) was associated with a shift in the chemistry of mucus towards a greater content of acidic glycoproteins; this would tend to make mucus more viscous.

4.5.1.2 Respiratory Region

a. Antimicrobial Activity

The development of an infectious disease requires both the presence of the appropriate pathogen and host vulnerability. The alveolar macrophage represents the main defense against pathogenic organisms depositing in the respiratory region of the lungs. The ability of acid aerosols to modify resistance to infection could result from a decreased ability to clear microbes, and a resultant increase in their residence time, due to alterations in normal macrophage function. To test this possibility, the rodent bacterial infectivity model has been used (Gardner and Graham, 1977). In this technique, mice are challenged with a bacterial aerosol after exposure to the pollutant of interest; mortality rate and survival time are then examined within a particular postexposure time period. Any decrease in the latter or increase in the former indicates impaired defense against respiratory infection. Studies that have used the infectivity model to assess effects of acid aerosols are outlined in Table 4-6. It is evident that these aerosols are apparently not very effective in enhancing susceptibility to bacterial-mediated respiratory disease. The only study that demonstrated any response was that of Coffin (1972), and increased mortality occurred only at an extremely high exposure level that likely resulted in extensive morphological damage.

In a related type of study, Fairchild et al. (1975b) examined the clearance rate of viable bacteria from the lungs of mice, using a colony count assay involving culturing ground lung tissue. They found that exposures (chamber) to 1.5 mg/m^3 of submicrometer (0.6 µm, CMD) H_2SO_4 for 1.5 h/d for 4 days prior to, or for 4 h after, exposure to a bacterial aerosol produced no alteration in the physical removal of this aerosol from the lungs. Since the bulk of microbial clearance was likely due to macrophage activity, these results are another, albeit indirect, indication that H_2SO_4 exposures at modest levels produce no measurable effect on bacterial infectivity.

TABLE 4-6. EFFECTS OF ACID AEROSOLS ON BACTERIAL INFECTIVITY IN MICE

Aerosol	Exposure Technique (Relative Humidity)	Mass Concentration (mg/m^3)	Aerosol Characteristics Size (μm)	Aerosol Characteristics σg	Exposure Duration	Response	Reference
H_2SO_4	chamber (38%)	0.9[a]	0.23 (VMD)	-	2h	nc[b]	Gardner et al. (1977)
H_2SO_4	head-only (31%)	0.543	0.08 (VMD)	2.3	2h	nc	Grose et al. (1982)
H_2SO_4	chamber	80	<1 (MMD)	-	3h	nc	Coffin (1972)
H_2SO_4	chamber	150	<1 (MMD)	-	3h	nc	Coffin (1972)
H_2SO_4	chamber	300	<1 (MMD)	-	3h	increased mortality	Coffin (1972)
H_2SO_4	head-only (31%)	0.365	0.06 (VMD)	2.3	2h/d, 5d	nc	Grose et al. (1982)
NH_4HSO_4	chamber	6.7	submicrometer	-	3h	nc	Ehrlich (1979)
$(NH_4)_2SO_4$	chamber	1.1 - 5.3	0.63 (MMD)	-	3h	nc[c]	Ehrlich et al. (1978)
$(NH_4)_2SO_4$	chamber	1	submicrometer	-	3h/d, 20d	nc	Aranyi et al. (1983)

[a] 1/3 of the concentration was reported to be associated with NH^{4+}.

[b] nc = no significant change from control.

[c] An increase in mortality was observed at the 2.1 to 3 mg/m^3 exposure level, but there was no relation between mortality and concentration in the study as a whole.

Macrophages are also involved in antiviral defense, but there are no data directly examining effects of acid on viral infectivity. In a study that examined this indirectly, macrophages harvested from mice exposed to submicrometer H_2SO_4 at very high levels (125 to 154 mg/m^3) for 10 to 14 days showed decreased interferon titers in the culture media (Schwartz et al., 1979); this suggests impaired resistance to viral infection.

b. Respiratory Region Clearance

There are only a few studies that examined the ability of acid aerosols to alter clearance of nonviable particles from the respiratory region. Rats exposed (nose-only) to 3.6 mg/m^3 H_2SO_4 (1 µm, MMAD) for 4 h showed a significant delay in clearance when the relative humidity of the exposure atmosphere was low (39%); no change in clearance was found when humidity was raised to 85% (Phalen et al., 1980). On the other hand, acceleration of clearance was seen in rabbits exposed for 1 h to H_2SO_4 at 1 mg/m^3 (80% RH; 0.3 µm, MMAD; $\sigma g = 1.6$) (Naumann and Schlesinger, 1986).

Some studies involving repeated exposures to acid aerosols have been reported. In one, rabbits were exposed (nose-only) to 0.25 mg/m^3 (0.3 µm, MMAD; $\sigma g = 1.7$) H_2SO_4 for 1 h/d, 5 d/wk, and tracer particles were administered on days 1, 57, and 240 following the start of the acid exposures (Schlesinger and Gearhart, 1986). Clearance (measured for 14 d after each tracer exposure) was found to be accelerated during the first test, and this acceleration was maintained throughout the acid exposure period. In another study (Schlesinger and Gearhart, 1987), rabbits were exposed (nose-only) 2 h/d for 14 days to 0.5 mg/m^3 H_2SO_4 (0.3 µm MMAD); retardation of respiratory region clearance of tracer particles administered on the first day of exposure was found. Schlesinger (1988) exposed rabbits to H_2SO_4 (0.3 µm, MMAD) at 0.25-1 mg/m^3 for 1-4 hr/d for 14 d. The results of this and the other two studies suggest a graded response which is dependent upon both exposure concentration and time; low values of CxT accelerate respiratory region clearance and high levels retard it, such as is seen with mucociliary transport following acute H_2SO_4 exposure (Schlesinger, 1988) and with respiratory region clearance after repeated exposures to other inhaled pollutants (Ferin and Leach, 1977; Driscoll et al., 1986).

The mechanisms responsible for the altered respiratory region clearance patterns seen in the above studies are not known. Observed clearance is the net consequence of a number of underlying responses; these likely include inflammation, epithelial lesions, release of specific mediators, and/or altered functioning of alveolar macrophages. The effects of acid aerosols on lung tissue have been previously discussed. There are only a few studies examining the response of macrophages, or the induction of inflammation following acid aerosol exposures.

In order to perform their role in clearance adequately, macrophages must be competent in a number of functions, e.g., phagocytosis, mobility, and attachment to a surface (Gardner, 1984). Alterations in any one, or combination, of these individual factors could perhaps result in altered clearance. Naumann and Schlesinger (1986) noted a reduction in surface adherence and an enhancement of phagocytosis in macrophages obtained by lavage from rabbits following a 1-h exposure (oral tube) to 1 mg/m^3 (0.3 μm, MMAD; $\sigma g = 1.6$) H_2SO_4. The acid exposure produced no change in the viability or numbers of recoverable macrophages. This is not surprising, since Coffin (1972) found no change in the number of recoverable macrophages from mice exposed to 300 mg/m^3 H_2SO_4 for 3 h.

In the only study with repeated H_2SO_4 exposures, macrophages were recovered by lavage from rabbits inhaling (nose-only) 0.5 mg/m^3 H_2SO_4 (0.3 μm, MMAD) for 2 h/d for up to 13 days (Schlesinger, 1987). Macrophage counts were increased after 2 of the daily exposures, but returned to control levels thereafter. Neutrophil counts remained at control levels throughout the study, indicating there to be no inflammatory response. Random mobility of macrophages was decreased after 6 and 13 of the exposures. The number of phagocytically active macrophages and the level of such activity was increased after 2 exposures, but phagocytosis became depressed by the end of the exposure series. Although such studies demonstrate that H_2SO_4 can alter macrophage function, they have not as yet been able to provide a complete understanding of the cellular mechanisms that may underlie the changes in respiratory region clearance observed with exposure to acid aerosols.

The relative potency of the acid sulfate aerosols in terms of altering respiratory region clearance was examined by Schlesinger (1988). Rabbits were exposed for 2 h/d for 14 d to 2 mg/m^3 $(NH_4)_2SO_4$ and to 0.5-2 mg/m^3 NH_4HSO_4. None of these exposures altered the clearance of tracer particles from the respiratory region measured during the exposure period. This contrasts with the retardation of clearance observed using similar exposures to 0.5 mg/m^3 H_2SO_4 (Schlesinger and Gearhart, 1987), suggesting that the response was likely due to H^+. However, the H^+ associated with the H_2SO_4 appeared to be more "potent" than that associated with NH_4HSO_4.

The role of relative acidity in altering macrophages has not been examined in any detail. Aranyi et al. (1983) found no change in total or differential counts of free cells lavaged from mice exposed (chamber) to submicrometer $(NH_4)_2SO_4$ at 1 mg/m^3 for 3 h/day for 20 days. Changes with H_2SO_4 were discussed above.

4.5.2 Immunologic Defense

Little is known about the effects of acid aerosols on humoral (antibody) or cell-mediated immunity. Since numerous antigens may be present in inhaled air, the possibility exists that air pollutants may enhance immunologic reaction and, thus, produce a more severe response and one with greater pulmonary pathogenic potential. Pinto et al. (1979) found that mice that inhaled H_2SO_4 (chamber; neither mass concentration nor particle size was specified) for 30 min daily and were then exposed weekly to a particulate antigen (sheep red blood cells) exhibited higher serum and bronchial lavage antibody titers than did animals exposed to the antigen alone. Other sulfate compound aerosols may also have this effect. Although none have been directly examined, SO_2 appears to have an adjuvant effect on antibody production (Matsumura, 1970). Pinto et al. (1979) also noted that the combination of acid with antigen produced a histopathologic response, characterized by mononuclear cell infiltration around the bronchi and blood vessels, while exposure to acid or antigen alone did not. Thus, the apparent adjuvant activity of H_2SO_4 may have been a factor promoting lung inflammation.

Osebold et al. (1980) exposed mice (chamber) to 1 mg/m^3 H_2SO_4 (0.04 µm, CMD; $\sigma g = 1.86$) to determine whether this enhanced the sensitization to an inhaled antigen (ovalbumin). The exposure regime involved intermittent 4 d exposures, with up to 16 total days of exposure; no increase in sensitization compared to controls was found. Kitabatake et al. (1979) exposed guinea pigs (head-only) to 1.91 mg/m^3 (<1 µm, MMAD) at 30-min intervals, twice per week, for 4 weeks, followed by up to 10 additional paired treatments with the H_2SO_4 for 30 min each, then exposure to aerosolized albumin for another 30 min. The breathing pattern of the animals was monitored for production of dyspnea, i.e., an "asthmatic attack." Enhanced sensitization was found after ~4 of the albumin exposures. A subsequent challenge with acetylcholine suggested hyperresponsive airways.

Acid aerosols may mediate the production of lung tumors. Godleski et al. (1984) examined the effect of inhaled $(NH_4)_2SO_4$ on benzo[a]pyrene (BaP)-induced carcinogenesis in hamster lung. Animals were exposed (chamber; 39 percent RH) to ~0.2 mg/m^3 $(NH_4)_2SO_4$ (0.3 μm, MMD; σg = 2.02), with or without instilled BaP, for 6 hr/d, 5 d/wk, for 15 wk; they were observed for an additional 2 yr. Exposure to $(NH_4)_2SO_4$ resulted in a significant reduction in tumor incidence during the first 6 mo of observation but, by 2 yr, there were no differences between those groups receiving BaP alone or BaP plus $(NH_4)_2SO_4$. These results indicated some interaction between BaP and sulfate, but not one that provided long-term protection against tumor development; they contrast with studies showing that $SO_4^=$ (administered by routes other than inhalation) did enhance the development of tumors induced by other carcinogens (Blunck and Crowther, 1975; DeBaun et al., 1970; Cohen and Bryan, 1978). These latter likely involved different metabolic and/or chemical reaction pathways; thus, it is possible that inhaled acid sulfates could enhance carcinogenesis resulting from materials other than BaP.

4.6 EFFECTS OF MIXTURES CONTAINING ACID AEROSOLS

Most of the toxicological data concerning effects of acid aerosols are derived from exposures using single compounds. Although these data are essential, it is also important to study responses that result from inhalation of typical combinations of materials, since general population exposures do involve mixtures. Toxicological interaction provides a basis whereby low concentrations of ambient pollutants may be damaging in combination. Thus, the lack of any toxic effect following exposure to an individual pollutant should always be interpreted with caution, since mixtures often behave differently than expected from the same pollutants acting separately. In this regard, the effects of acid aerosols may be influenced by various co-pollutants. Table 4-7 presents a survey of studies examining various endpoints following exposures to mixed atmospheres containing acid aerosols. Most of the studies listed involved inhalation of atmospheres containing only two pollutants. Investigations using more complex atmospheres are discussed separately.

The occurrence or extent of any toxicological interaction involving acid aerosols depends on the endpoint being examined, as well as on the co-inhalant. For example, in most studies that employed acid with O_3, the response was due

TABLE 4-7. TOXICOLOGIC INTERACTIONS TO MIXTURES CONTAINING ACID AEROSOLS

Exposure Atmosphere	Exposure Technique (Relative Humidity)	Exposure Duration	Experimental Animal	Endpoints	Interaction	Reference
H_2SO_4 (9.98 mg/m^3, 0.83 µm AED, σg = 1.7) + O_3 (0.52 ppm)	chamber (56%)	6h/d, 5d/wk, 6mo	rat guinea pig	morphology	none: response due to O_3	Cavender et al. (1978)
H_2SO_4 (1 mg/m^3, 0.036 µm CMD, σg = 1.8) + O_3 (0.5 ppm)	chamber (50%)	continuous, up to 180d	rat	morphology	none: response due to O_3	Moore and Schwartz (1981)
H_2SO_4 (2 mg/m^3, 0.3 µm MMD, σg = 2.5) + O_3 (0.9 ppm)	chamber (40-60%)	8h/d, 82d	rat	morphology	none: response due to O_3	Juhos et al. (1978)
H_2SO_4 (5-10 mg/m^3, 0.75-1.01 µm MMD) + O_3 (1-2 ppm)	chamber (55%)	2d, 7d	rat guinea pig	morphology	none: response due to O_3	Cavender et al. (1977b)
H_2SO_4 (0.04-1 mg/m^3, 0.4-0.5 µm MMAD, σg = 2) + O_3 (0.12-0.64 ppm)	chamber (70-80%)	6h to 7d	rat	lavageable protein content of lungs	synergism at $\geq$0.1 mg/m^3 H_2SO_4 + $\geq$0.2 ppm O_3	Warren and Last (1987)
		5d-9d	rat	tissue protein content of lungs	synergism at 1 mg/m^3 H_2SO_4 + 0.64 ppm O_3; 0.1 mg/m^3 H_2SO_4 + 0.2 ppm O_3	Warren and Last (1987)
		7d	rat	collagen synthesis rate by lung minces	synergism at $\geq$0.2 mg/m^3 H_2SO_4 + 0.64 ppm O_3; and $\geq$0.04 mg/m^3 H_2SO_4 + 0.2 ppm O_3	Warren and Last (1987)
H_2SO_4 (3.6 mg/m^3, 1 µm MMAD, σg = ~2) + O_3 (0.79 ppm)	nose-only (39%; 85%)	4h	rat	clearance: tracheobronchial, respiratory regions	none: effect due to O_3	Phalen et al. (1980)
H_2SO_4 (1.1 mg/m^3, 0.5 µm) + O_3 (0.5 ppm)	chamber	3d,14d (23.5 h/d)	rat	tracheal mucus glycoprotein secretion	synergism: no effect of either alone	Last and Cross (1978)
H_2SO_4 (0.011 mg/m^3, 0.5 µm) + O_3 (0.5 ppm)	chamber	3d (23.5 h/d)	rat	tracheal mucus glycoprotein secretion	synergism: no effect of either alone	Last and Cross (1978)

(continued on the following page)

TABLE 4-7. (continued)

Exposure Atmosphere	Exposure Technique (Relative Humidity)	Exposure Duration	Experimental Animal	Endpoints	Interaction	Reference
H_2SO_4 (0.847 mg/m^3, 0.2 µm CMD, σg = 2.1) + O_3 (0.1 ppm)	chamber (33%)	3h	hamster	cilia beat frequency in explants trachea	none	Grose et al. (1982)
H_2SO_4 (0.241 or 0.483 mg/m^3, 0.2 µm, σg = 2.1) + O_3 (0.1 ppm)	chamber (33%)	3h	mouse	bacterial infectivity	synergism	Grose et al. (1982)
H_2SO_4 (1 mg/m^3, 0.04 CMD, σg = 1.86) + O_3 (0.5 ppm)	chamber	intermittent exposure; 16 exposures in 4d sets	mouse	sensitization to inhaled antigen	possible synergism	Osebold et al. (1980)
H_2SO_4 (0.11-0.97 mg/m^3, 0.64-1.07 µm MMD, σg = 1.5-4.8 + SO_2 (1-5 ppm); or + Fly ash (0.5 mg/m^3, 5-6 µm MMD); or + SO_2 + Fly ash	chamber (50%)	78wk	cynomolgous monkey	morphology	none: response due to H_2SO_4	Alarie et al. (1975)
H_2SO_4 (0.9 mg/m^3, 90% <0.5 µm (MMAD) + SO_2 (5.1 ppm)	chamber (43-50%)	21h/d, 620d	dog	pulmonary function	none: response due either to SO_2 or H_2SO_4	Lewis et al. (1973)
H_2SO_4 (0.835 mg/m^3, 90% <0.5 µm + SO_2 (5.1 ppm)	chamber (43-50%)	21h/d, 225d	dog	pulmonary function	mixture reduced DL_{co} greater than H_2SO_4 alone (no SO_2 control)	Lewis et al. (1969)
H_2SO_4 (0.1 mg/m^3, 1 µm MMAD) + SO_2 (0.2 ppm)	head-only	1h	guinea pig	pulmonary function	additive	Amdur (1974)
H_2SO_4 (1.89 mg/m^3 <1 µm MMAD) + SO_2 (145 ppm)	head-only	0.5h, twice weekly for 4 weeks; then 0.5h twice weekly with antigen or constrictor challenge	guinea pig	sensitization to inhaled antigen (albumin); responsivity to acetylcholine	enhanced response compared to H_2SO_4 alone	Kitabatake et al. (1979)
H_2SO_4 (0.5 mg/m^3, 0.3 µm MMAD, σg = 1.6) + NO_2 (0.3, 1 ppm)	nose-only (60%)	2h/d, 5d/wk, 14d	rabbit	clearance-respiratory region	none @ 0.3 ppm: response due to H_2SO_4; at 1 ppm: response different from both NO_2 or H_2SO_4	Schlesinger and Gearhart (1987)

(continued on the following page)

TABLE 4-7. (continued)

Exposure Atmosphere	Exposure Technique (Relative Humidity)	Exposure Duration	Experimental Animal	Endpoints	Interaction	Reference
H_2SO_4 (0.89 mg/m^3, 0.4 μm MMAD, σg = 2.16) + NO_2 (4.9 ppm)	chamber	7d (23.5 h/d)	rat	collagen synthesis by lung minces	synergism	Last and Warren (1987)
H_2SO_4 (0.52 mg/m^3, 0.4 μm MMAD, σg = 1.76) + NO_2 (4.7 ppm)	chamber	1,3d (23.5 h/d)	rat	protein content of lavage fluid	synergism 1d	Last and Warren (1987)
H_2SO_4 (1, 10, 100 mg/m^3, 0.8 μm MMAD, σg = 1.7-1.8) + fly ash (70 mg/m^3, 6 μm MMAD)	chamber	6h	rat	lavage indices (LDH, acid phosphatase, glutathione reductase	minimal interaction: response largely due to H_2SO_4; increase in LDH and glutathione reductase only in combined exposure	Henderson et al. (1980a)
H_2SO_4 (0.08 mg/m^3, 0.5 or 2.2 μm MMD, σg = 1.6-4.3) + fly ash (0.45 mg, 3.5-5.3 μm MMD)	chamber	52wk (22-23 h/d)	guinea pig	morphology	none	Alarie et al. (1975)
H_2SO_4 (1.1 mg/m^3, 0.12 μm CMD) + carbon particles 1.5 mg/m^3, 0.3 μm CMD) [acid-coated carbon: 0.4 μm]	chamber (60%)	3h	hamster	cilia beat frequency in explants (trachea)	none: response due to acid (some enhancement in morphologic response with mixture)	Schiff et al. (1979)
H_2SO_4 (1.4 mg/m^3, 0.12 μm CMD) + carbon particles (1.5 mg/m^3, 0.3 μm CMD) [acid-coated carbon: 0.4 μm]	chamber (60%)	3h/d, 5d/wk up to 20wk	mouse	bacterial infectivity	none: effect due to carbon	Fenters et al. (1979)
				morphology	none: effect due to carbon	
				viral infectivity	enhancement compared to carbon	
				immunoglobulin level (serum)	none	
NH_4HSO_4 (0.9 mg/m^3, 0.1 μm MMD) + SO_2 (0.32 ppm)	head-only (50%)	1h	guinea pig	pulmonary function	additive	Amdur et al. (1978b)
$(NH_4)_2SO_4$ (5 mg/m^3, 0.5 μm MMAD, σg = 1.7-1.9) + O_3 (0.60-0.99 ppm)	chamber (70-80%)	up to 14d	rat	cell no. (macrophage, fibroblast)	synergism: by 3d	Last et al. (1984)
				morphology	synergism	Last et al. (1984)

(continued on the following page)

TABLE 4-7. (continued)

Exposure Atmosphere	Exposure Technique (Relative Humidity)	Exposure Duration	Experimental Animal	Endpoints	Interaction	Reference
$(NH_4)_2SO_4$ (0.484 mg/m^3, 0.53 μm MMAD) + O_3 (0.99 ppm)	chamber (80%)	7d (23.5 h/d)	rat	collagen synthesis by lung minces	synergism	Last et al. (1986)
$(NH_4)_2SO_4$ (3.6 mg/m^3, 0.4 μm MMAD, σg = ~2) + O_3 (0.79)	nose-only (39%, 85%)	4h	rat	clearance: tracheobronchial and respiratory region	none: effect due to O_3	Phalen et al. (1980)
$(NH_4)_2SO_4$ (5 mg/m^3, 0.5 μm MMAD, σg = 1.7) + O_3 (0.2, 0.64 ppm)	chamber (70-80%)	7d (23.5 h/d)	rat	lavageable protein	synergism at $\geq$0.2 ppm O_3	Warren et al. (1986)
				tissue protein	none	Warren et al. (1986)
				collagen synthesis rate by lung minces	synergism at $\geq$0.2 ppm O_3	Warren et al. (1986)
$(NH_4)_2SO_4$ (0.5 mg/m^3, 0.1 μm MMD) + SO_2 (0.3 ppm)	head-only (50%)	1h	guinea pig	pulmonary function	additive	Amdur et al. (1978b)
$(NH_4)_2SO_4$ (5 mg/m^3, 0.8-1 μm MMAD σg = 1.8-2) + NO_2 (5.3, 2.6.5 ppm)	chamber	7d	rat	collagen synthesis in lung minces	synergism	Last et al. (1983)

solely to the latter rather than to the former. The major exceptions are the studies of Last and colleagues (see Table 4-7), in which O_3 and H_2SO_4 were synergistic in altering lung protein content and collagen synthesis, and that of Osebold et al. (1980), in which the inclusion of H_2SO_4 potentiated the response to inhaled antigen seen with O_3 alone. This latter study suggests that inhalation of pollutant mixtures containing acid aerosols may increase the number of sensitized individuals, or augment a reaction in those already sensitized. These studies are highly suggestive that H_2SO_4 acts by increasing the effective dose of O_3 delivered to its target site(s) in the lungs.

Although most interaction studies involve simultaneous exposure to more than one pollutant, exposure to one substance may alter the response to another subsequently inhaled. Thus, the order of exposure to inhaled materials may be important in eliciting a toxic interaction. For example, using sequential exposures (chamber), Gardner et al. (1977) found an additive increase in infectivity when mice were exposed to 0.1 ppm O_3 for 3 h immediately before exposure to 0.9 mg/m^3 (0.2 µm, VMD) H_2SO_4 for 2 h; no difference from control was found when the H_2SO_4 was administered prior to the O_3. On the other hand, Silbaugh and Mauderly (1986), using bronchoconstriction as the endpoint, found that a 2 h exposure (chamber, 65 to 72 percent RH) of guinea pigs to 0.8 ppm O_3 did not alter the response to a subsequent 1-hr exposure to 12 mg/m^3 (0.63 µm, MMAD) H_2SO_4. Grose et al. (1980) exposed hamsters (chamber) to 0.1 ppm O_3 for 3 h followed by 1.09 mg/m^3 (0.3 µm, VMD) H_2SO_4 for 2 h. A reduction in ciliary activity in isolated tracheal cultures was observed, but the magnitude of the change was significantly less than that found with exposure to the H_2SO_4 alone; O_3 alone produced no change at all.

Another factor which may influence the interaction between acid aerosols and other inhaled materials is the particle size of the former. Using pulmonary resistance in guinea pigs as the endpoint, Amdur (1957) found a synergistic response following a 1-h inhalation (head-only) of 82 ppm SO_2 with 19 mg/m^3 of 0.8 µm (MMD) H_2SO_4; on the other hand, no synergism was seen when inhalation involved a 2.5 µm acid droplet. Last et al. (1986) observed a synergistic response on biochemical indices in rat lung with exposure (chamber, 80 percent RH) to H_2SO_4 (1 mg/m^3) and O_3 (0.6 ppm) when the droplet size was 0.5 µm (MMAD), while no potentiation of O_3 response was seen with a droplet size of 0.03 µm. Apparently, in this case, the aerosol that had greater deposition in the terminal-respiratory bronchiolar region (the major site of O_3 deposition) was most interactive with O_3.

The pollutant atmosphere in most environments is a complex mix of more than two materials. A few studies have attempted to examine the effects of multicomponent atmospheres containing acid particles. Mannix et al. (1982) examined the effects of a 4 h exposure (chamber) of rats to a SO_2-sulfate mix, consisting of SO_2 (5 ppm) plus 1.5 mg/m^3 (0.5 µm, MMAD, $\sigma g = 1.6$) of an aerosol containing $(NH_4)_2SO_4$ and $Fe_2(SO_4)_3$. No change in particle clearance from the tracheobronchial tree or respiratory region was found. Aranyi et al. (1983) exposed mice (chamber; 48 to 54 percent RH; 5 h/d, 5 d/wk for 103 d) to mixtures of O_3 (0.1 ppm), SO_2 (5 ppm) and $(NH_4)_2SO_4$ (1.04 mg/m^3; 0.39 µm MMAD; σg 2.42), and noted enhanced bactericidal activity of macrophages, compared to O_3 alone. This same exposure regime also resulted in a greater (compared to O_3 alone) degree of _in vitro_ cytostasis to tumor target cells cocultured with peritoneal macrophages obtained from exposed mice. The investigators suggested that these results indicated possible macrophage activation by the complex atmosphere.

Hyde et al. (1978) exposed dogs (in chambers) for 16 hr/d for 68 mo to pollutant mixtures as follows: H_2SO_4 (0.09 mg/m^3, <0.5 µm) + SO_2 (0.4 ppm); H_2SO_4 (0.09 mg/m^3) + SO_2 (0.46 ppm) + auto exhaust; H_2SO_4 (0.11 mg/m^3) + SO_2 (0.4 ppm) + irradiated auto exhaust (which results in production of oxidants); nonirradiated auto exhaust; or irradiated auto exhaust. The animals were examined for morphological damage 32 to 36 mo after exposures ended. Although there was no evidence of any interaction between auto exhaust and sulfur oxides, most groups showed enlargements of air spaces in proximal acini and hyperplasia of bronchiolar cells. Pulmonary function changes were also observed in these animals (Stara et al., 1980). Unfortunately, the individual component(s) of the mixtures causing these effects could not be determined.

Kleinman et al. (1985a,b) exposed rats (nose-only) for 4 h to atmospheres consisting of various combinations of O_3 (0.6 ppm), NO_2 (2.5 ppm), SO_2 (5 ppm) and aerosol. The latter consisted of 1 mg/m^3 (0.2 µm, MMAD) of either $(NH_4)_2SO_4$ or H_2SO_4, laced with iron and manganese sulfates. The metallic salts act as catalysts for the conversion of sulfur (IV) into sulfur (VI), and the incorporation of gases into the aerosol droplets. The respiratory region was examined for morphological effects. A confounding factor in these studies was the production of nitric acid in atmospheres that contained O_3 and NO_2, and nitrate in those that contained O_3 and $(NH_4)_2SO_4$ but not NO_2. Nevertheless, a significant enhancement of tissue damage was produced by exposure to atmospheres containing H_2SO_4 (or HNO_3) compared to those containing $(NH_4)_2SO_4$. In addition, there was a suggestion that the former atmospheres resulted in a greater area of the lung becoming involved in lesions, which were characterized by a thickening of alveolar walls, cellular infiltration in the interstitium and an increase in free cells within alveolar spaces. Exercise seemed to potentiate the histological response to the complex mixture containing H_2SO_4 (Kleinman et al., 1988).

Mautz et al. (1985) examined the effects of complex mixtures upon pulmonary mechanics in exercising dogs. Exposures (nose-only) were for 200 min to atmospheres consisting of O_3 (0.45 to 0.7 ppm), SO_2 (4.8 to 5.2 ppm), H_2SO_4 (0.8 to 1.2 mg/m^3, 0.2 µm MMAD), and catalytic salts (iron and manganese sulfates). A greater increase in resistance and decrease in compliance was found with the complex atmospheres containing the sulfate compounds than with O_3 alone. Although this was ascribed to the presence of the H_2SO_4, synergism could not be definitively concluded since the mixture was not tested without O_3.

Most of the toxicologic data base for H_2SO_4 consists of studies aimed at assessing the effects of exposure to submicrometer aerosols such as would be formed secondarily in the atmosphere from SO_2. Recently, the response to sulfuric acid coating the surface of metallic oxide particles was examined by Amdur and Chen (1988); this was intended to simulate primary emissions from coal combustion processes. Guinea pigs were exposed for 3 hr/day for 5 days to ultrafine (0.05 µm CMD, $\sigma g = 2$) aerosols of zinc oxide (ZnO), which contained a surface coating of H_2SO_4. Levels as low as 0.20-0.30 mg/m^3 as equivalent H_2SO_4 delivered in this manner resulted in significant reductions in total lung volume, vital capacity, and CO diffusing capacity. The effects appeared to be cumulative, in that their severity increased with increasing days of exposure. These exposures also resulted in an increase in the protein content of pulmonary lavage fluid (an index of lung damage) as well as an increase in neutrophils (and index of inflammation). The investigators found that much higher exposure levels of pure H_2SO_4 aerosol were needed to produce comparable results. This suggests that the physical state of the associated acid in pollutant mixtures is an important determinant of response.

It is apparent from this survey of the data base that toxicologic interactions with acid aerosols may be antagonistic, additive, or synergistic. The latter poses the greatest threat in terms of potential health effects.

There are various mechanisms by which synergism may occur. One is physical, the result of adsorption of one material onto the acid particle and subsequent transport to more sensitive sites, or sites where this material normally would not deposit in concentrated amounts. The acid particles, thus, essentially act as carriers. A second mechanism involves dissolution and reaction within an acid droplet, forming some secondary product(s) that may be more toxicologically active than the primary materials.

A third mechanism may involve an acid induced change in the local microenvironment of the lung, enhancing the effects of the co-inhalant. This was proposed by Last and colleagues based upon a series of studies (Last et al., 1983, 1984, 1986; Last and Cross, 1978; Warren and Last, 1987; Warren et al., 1986) in which rats were exposed to sulfate aerosols (H_2SO_4, $(NH_4)_2SO_4$, Na_2SO_4) with and without oxidant gases (O_3 or NO_2), and various biochemical endpoints examined. Acidic sulfate aerosols alone did not produce any response at levels that caused a response in conjunction with O_3 or NO_2. The investigators suggested that the deposition of the acid aerosol produced a shift in local pH within the alveolar milieu; this shift then resulted in a change in the reactivity or residence time of reactants (e.g., radicals) involved in oxidant-induced pulmonary effects. Further evidence that the toxic interaction was due to acidity was the finding that neither Na_2SO_4 nor NaCl was synergistic with O_3 (Last et al., 1986).

4.8 SUMMARY AND CONCLUSIONS

The bulk of the toxicologic data base on acid aerosols involves sulfate compound particles, primarily submicrometer H_2SO_4. There are no data for larger H_2SO_4 droplets that would be constituents of acid fogs, and few data for other, nonsulfur constituents of such fogs or other acidic atmospheres, e.g., nitrogen compounds such as HNO_3. However, the available evidence indicates that the observed responses to acid sulfates are likely due to H^+ rather than to $SO_4^=$. Thus, H_2SO_4 may be considered to be a "model" acidic irritant and the observed effects seen for this pollutant likely apply, at least qualitatively, to other acid aerosols having similar deposition patterns in the respiratory tract. However, it has been suggested that the irritant potency of an acid may be related more to its total H^+ concentration, i.e., titratable acidity, rather than to its free H^+ concentration as measured by pH (Fine et al., 1987). This implies that the specific chemical composition of different acids may be a factor mediating the quantitative response. In any case, the toxicity of H_2SO_4 is likely due to the direct irritant action of deposited acid droplets and/or to the subsequent release of humoral mediators such as histamine.

A survey of the data base for H_2SO_4 toxicology shows what often appear to be contradictory or, at the least, variable results. There are a number of possible explanations for these. A major one involves response differences between animal species (or strains) due to intrinsic sensitivity differences, or differences in age, aerosol deposition pattern, and respiratory tract NH_3 levels. Various experimental variables (e.g., relative humidity), mode of exposure, aerosol particle size, exogenous NH_3 levels, also differ in different studies. But in spite of such differences, a number of generalizations regarding the toxicology of H_2SO_4 may be made, based upon relative consistencies in similar studies.

The available evidence indicates that H_2SO_4 exerts its action throughout the respiratory tract, with the type and magnitude of response dependent upon particle size, mass concentration, and, for most endpoints, exposure duration. At very high concentrations (>15 mg/m^3), mortality will occur following acute exposure, due primarily to laryngeal or bronchoconstriction; larger particles are more effective in this regard than are smaller ones. Somewhat lower exposure levels will also result in death, but this is due to extensive pulmonary damage, including edema, hemorrhage, epithelial desquamation, and atelectasis. But even in the most sensitive species, LD_0 levels are quite high (>8 mg/m^3)

Both acute and chronic exposure to H_2SO_4 at levels well below lethal ones will produce functional changes in the respiratory tract. The pathological significance for some of these is greater than for others. Acute exposure will alter pulmonary function, largely due to bronchoconstrictive action. However, attempts to produce changes in airway resistance in healthy animals at levels below 1 mg/m^3 have been largely unsuccessful, except in the guinea pig. The lowest effective level of H_2SO_4 producing bronchoconstriction to date in the guinea pig is 0.1 mg/m^3 (1 h exposure). In general, the smaller-size droplets were more effective in altering pulmonary function, especially at low concentrations. Yet even in this species, there are inconsistencies in the type of response exhibited towards acid aerosols. Some studies show an exposure-concentration response beginning at 0.1 mg/m^3, while others show an all-or-none response beginning only at concentrations much higher than this, and no response at lower levels. Chronic exposure to H_2SO_4 is also associated with alterations in pulmonary function, e.g., changes in the distribution of ventilation and in respiratory rate in monkeys. But, in these cases, the effective concentrations are $\geq$0.5 mg/m^3.

The relationship between the above changes in pulmonary function and disease is unclear. But the development of hyperresponsive airways in healthy animals due to acid aerosols, at levels below those producing any change in lung functional indices without bronchoconstrictor challenge, does have implications for the pathogenesis of airway disease due to nonspecific irritant exposure. Hyperresponsive airways have been induced in rabbits with repeated exposures to 0.25 mg/m^3 H_2SO_4; the effects on responsivity of long-term exposure to lower levels are not known.

Severe morphologic alterations in the respiratory tract will occur at high acid levels. At low levels, and with chronic exposure, the main response seems to be hypertrophy and/or hyperplasia of mucus secretory cells in the epithelium; these alterations may extend to the small bronchi and bronchioles, where secretory cells are normally rare or absent. This likely results in an increase in secretory rate and mucus volume in such airways, which is a possible factor in the pathogenesis of obstructive lung disease.

The lungs have an array of defense mechanisms to detoxify and physically remove inhaled material, and available evidence indicates that certain of these defenses may be altered by exposure to H_2SO_4 at levels <1 mg/m^3. Defenses such as resistance to bacterial infection are not altered even by acute exposure to concentrations as high as 150 mg/m^3. However, the bronchial mucociliary clearance system is very sensitive to inhaled acids; much lower levels of H_2SO_4 (<1 mg/m^3) produce alterations in mucociliary transport rates in healthy animals. The lowest level shown to have such an effect, 0.1 mg/m^3 with repeated exposures in the donkey, is well below concentrations that result in other physiological changes in most experimental animals. Furthermore, exposures to somewhat higher concentrations that also alter clearance have been associated with various morphometric changes in the bronchial tree indicative of mucus hypersecretion.

Limited data also suggest that exposure to acid aerosols may affect the functioning of alveolar macrophages; the lowest level examined in this regard is 0.5 mg/m^3 H_2SO_4. Although the pathogenic implications of such effects are not certain, they likely play some role in altering removal of material from the respiratory region. Respiratory region particle clearance is affected by repeated H_2SO_4 exposures to as low as 0.25 mg/m^3.

Effective clearance mechanisms are critical in reducing the residence time of inhaled, deposited materials, and alterations in clearance, especially due to chronic acid aerosol exposure, may be associated with lung disease. Mucociliary efficiency influences the development of acute infectious disease (Proctor, 1979; Niederman et al., 1983), and there is accumulating evidence that dysfunction of bronchial clearance plays a role in the pathogenesis of chronic bronchitis (Albert et al., 1973; Schlesinger et al., 1983) and may be an early indication of disease in otherwise asymptomatic individuals (Mossberg and Camner, 1980; Goodman et al., 1978).

The role of acid aerosols, specifically H_2SO_4, in the development of chronic bronchitis is supported by a comparison of results from studies of submicrometer H_2SO_4 mist and cigarette-smoke exposures (Lippmann et al., 1982); the latter are known to be involved in the etiology of human chronic bronchitis. The effects of both agents on bronchial mucociliary clearance patterns were found to be essentially the same following either single or intermittent exposures in experimental animals and humans.

The pathogenic implications of alterations in clearance from the respiratory region are more speculative than those for mucociliary clearance, but clearance rates are reduced in humans with chronic obstructive lung disease and in cigarette smokers (Bohning et al., 1982; Cohen et al., 1979). This suggests some relation between altered defense and chronic lung disease development in these latter individuals; the results of toxicologic assessments suggest the former precedes the latter.

The assessment of the toxicology of acid aerosols requires some examination of potential interactions with other air pollutants. Although such interactions may be antagonistic, additive, or synergistic, the exact mechanism by which they occur is not well defined, and evidence for them may depend upon the sequence of exposure as well as on the endpoint examined. Low levels of H_2SO_4 (0.04 mg/m^3) have been shown to react synergistically with O_3 in simultaneous exposures using biochemical endpoints. In this case, the H_2SO_4

enhanced the damage due to the O_3. This is common in studies with O_3, while H_2SO_4 toxic effects themselves may be more directly manifest with other, less potent, co-inhalants. There is some evidence that sulfuric acid existing as a sulfate coating on other particles may be more potent than the acid existing as a sulfate droplet. The most realistic exposures are to multicomponent atmospheres, but the results of these are often difficult to assess due to chemical interactions between the components and a resultant lack of precise control over the ultimate composition of the exposure environment.

In conclusion, the acute effects of acid (i.e. H_2SO_4) inhalation involve, at high levels, bronchoconstriction and, at lower levels, alterations in the rate of clearance from the tracheobronchial tree and pulmonary region. The toxicologic data base also allows for speculation that the potential does exist for the production of chronic lung disease due to long-term inhalation of acid aerosol, i.e., H_2SO_4. The diseases most likely to be associated with such exposures are asthma and chronic bronchitis. The greatest potential health threat due to pollutant interactions likely involves O_3, since synergism has been found with combinations of peak ambient levels of O_3 (0.2 ppm) and H_2SO_4 (0.04 mg/m^3); in this case, the associated disease is speculated to be pulmonary fibrosis. However, the lowest level of acid capable of eliciting responses (alone or in combination with other pollutants) is currently not known.

4.9 REFERENCES

Alarie, Y.; Busey, W. M.; Krumm, A. A.; Ulrich, C. E. (1973) Long-term continuous exposure to sulfuric acid mist in cynomolgus monkeys and guinea pigs. Arch. Environ. Health 27: 16-24.

Alarie, Y. C.; Krumm, A. A.; Busey, W. M.; Ulrich, C. E.; Kantz, R. J., II. (1975) Long-term exposure to sulfur dioxide, sulfuric acid mist, fly ash, and their mixtures: results of studies in monkeys and guinea pigs. Arch. Environ. Health 30: 254-262.

Albert, R. E.; Lippmann, M.; Peterson, H. T., Jr.; Berger, J.; Sanborn, K.; Bohning, D. (1973) Bronchial deposition and clearance of aerosols. Arch. Intern. Med. 131: 115-127.

Amdur, M. O. (1957) The influence of aerosols on the respiratory response of guinea pigs to sulfur dioxide. Am. Ind. Hyg. Assoc. Q. 18: 149-155.

Amdur, M. O. (1958) The respiratory response of guinea pigs to sulfuric acid mist. Arch. Ind. Health 18: 407-414.

Amdur, M. O. (1971) Aerosols formed by oxidation of sulfur dioxide: review of their toxicology. Arch. Environ. Health 23: 459-468.

Amdur, M. O. (1974) 1974 Cummings memorial lecture: the long road from Donora. Am. Ind. Hyg. Assoc. J. 35: 589-597.

Amdur, M. O.; Schulz, R. Z.; Drinker, P. (1952) Toxicity of sulfuric acid mist to guinea pigs. Arch. Ind. Hyg. Occup. Med. 5: 318-329.

Amdur, M. O.; Dubriel, M.; Creasia, D. A. (1978a) Respiratory response of guinea pigs to low levels of sulfuric acid. Environ. Res. 15: 418-423.

Amdur, M. O.; Bayles, J.; Ugro, V.; Underhill, D. W. (1978b) Comparative irritant potency of sulfate salts. Environ. Res. 16: 1-8.

Amdur, M. O.; Chen, L. C. (1988) Furnace generated acid aerosols: speciation and pulmonary effects. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Aranyi, C.; Vana, S. C.; Thomas, P. T.; Bradof, J. N.; Fenters, J. D.; Graham, J. A.; Miller, F. J. (1983) Effects of subchronic exposure to a mixture of O_3, SO_2 and $(NH_4)_2SO_4$ on host defenses of mice. J. Toxicol. Environ. Health 12: 55-71.

Bates, D. V.; Sizto, R. (1986) A study of hospital admissions and air pollutants in southern Ontario. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment and control strategies: proceedings of the 2nd US-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 767-777.

Blunck, J. M.; Crowther, C. E. (1975) Enhancement of azo dye carcinogenesis by dietary sodium sulphate. Eur. J. Cancer 11: 23-31.

Bohning, D. E.; Atkins, H. L.; Cohn, S. H. (1982) Long-term particle clearance in man: normal and impaired. Ann. Occup. Hyg. 26: 259-271.

Bowden, D. H. (1984) The alveolar macrophage. EHP Environ. Health Perspect. 55: 327-341.

Breuninger, H. (1964) Ueber das physikalisch-chemische Verhalten des Nasenschleims [The physical-chemical suppression of nasal mucous]. Arch. Ohren Nasen Kehlkopfheilkd. 184: 133-138.

Brownstein, D. G. (1980) Reflex-mediated desquamation of bronchiolar epithelium in guinea pigs exposed acutely to sulfuric acid aerosol. Am. J. Pathol. 98: 577-590.

Busch, R. H.; Buschbom, R. L.; Cannon, W. C.; Lauhala, K. E.; Miller, F. J.; Graham, J. A.; Smith, L. G. (1984) Effects of ammonium sulfate aerosol exposure on lung structure of normal and elastase-impaired rats and guinea pigs. Environ. Res. 33: 454-472.

Busch, R. H.; Buschbom, R. L.; Cannon, W. C.; Lauhala, K. E.; Miller, F. J.; Graham, J. A.; Smith, L. G. (1986) Effects of ammonium nitrate aerosol exposure on lung structure of normal and elastase-impaired rats and guinea pigs. Environ. Res. 39: 237-252.

Bushtueva, K. A. (1957) On the toxicology of H_2SO_4 aerosol. Gig. Sanit. (22): 17-22.

Cavender, F. L.; Steinhagen, W. H.; McLaurin, D. A., III; Cockrell, B. Y. (1977a) Species difference in sulfuric acid mist inhalation. Am. Rev. Respir. Dis. 115(suppl.): 204.

Cavender, F. L.; Steinhagen, W. H.; Ulrich, C. E.; Busey, W. M.; Cockrell, B. Y.; Haseman, J. K.; Hogan, M. D.; Drew, R. T. (1977b) Effects in rats and guinea pigs of short-term exposures to sulfuric acid mist, ozone, and their combination. J. Toxicol. Environ. Health 3: 521-533.

Cavender, F. L.; Singh, B.; Cockrell, B. Y. (1978) Effects in rats and guinea pigs of six-month exposures to sulfuric acid mist, ozone, and their combination. J. Toxicol. Environ. Health 4: 845-852.

Charles, J. M.; Menzel, D. B. (1975) Ammonium and sulfate ion release of histamine from lung fragments. Arch. Environ. Health 30: 314-316.

Chen, L. C.; Schlesinger, R. B. (1983) Response of the bronchial mucociliary clearance system in rabbits to inhaled sulfite and sulfuric acid aerosols. Toxicol. Appl. Pharmacol. 71: 123-131.

Cockrell, B. Y.; Busey, W. M.; Cavender, F. L.. (1978) Respiratory tract lesions in guinea pigs exposed to sulfuric acid mist. J. Toxicol. Environ. Health 4: 835-844.

Coffin, D. L. (1972) Interaction of infectious disease and air pollutants: influence of "tolerance." In: Lee, D. H. K., ed. Environmental factors in respiratory disease: Fogarty International Center proceedings no. 11; Baltimore, MD. New York, NY: Academic Press; pp. 151-173. (Lee, D. H. K.; Hewson, E. W.; Okun, D., eds. Environmental sciences: an interdisciplinary monograph series).

Cohen, S. M.; Bryan, G. T. (1978) Effect of p-hydroxyacetanilide, sodium sulfate, and L-methionine on the leukemogenicity of N-[4-(5-nitro-2-furyl)-2-thioazolyl]acetamide. Cancer Res. 38: 1398-1405.

Cohen, D.; Arai, S. F.; Brain, J. D. (1979) Smoking impairs long-term dust clearance from the lung. Science (Washington, DC) 204: 514-517.

Cosio, M. D.; Ghezzo, H.; Hogg, J. C.; Corbin, R.; Loveland, M.; Dosman, J.; Macklem, P. T. (1978) The relations between structural changes in small airways and pulmonary-function tests. N. Engl. J. Med. 298: 1277-1281.

DeBaun, J. R.; Smith, J. Y. R.; Miller, E. C.; Miller, J. A. (1970) Reactivity in vivo of the carcinogen N-hydroxy-2-acetylaminofluorene: increase by sulfate ion. Science (Washington, DC) 167: 184-186.

Driscoll, K. E.; Vollmuth, T. A.; Schlesinger, R. B. (1986) Early alveolar clearance of particles in rabbits undergoing acute and subchronic exposure to ozone. Fundam. Appl. Toxicol. 7: 264-271.

Ehrlich, R. (1979) Interaction between environmental pollutants and respiratory infections. In: Gardner, D. E.; Hu, E. P. C.; Graham, J. A. eds. Proceedings of the symposium on experimental models for pulmonary research; February; Hilton Head Island, NC. Research Triangle Park, NC: U. S. Environmental Protection Agency, Inhalation Toxicology Branch; EPA report no. EPA-600/9-79-022. Available from: NTIS, Springfield, VA; PB80-121049.

Ehrlich, R.; Findlay, J. C.; Gardner, D. E. (1978) Susceptibility to bacterial pneumonia of animals exposed to sulfates. Toxicol. Lett. 1: 325-330.

Fairchild, G. A.; Stultz, S.; Coffin, D. L. (1975a) Sulfuric acid effect on the deposition of radioactive aerosol in the respiratory tract of guinea pigs. Am. Ind. Hyg. Assoc. J. 36: 584-594.

Fairchild, G. A.; Kane, P.; Adams, B.; Coffin, D. (1975b) Sulfuric acid and streptococci clearance from respiratory tracts of mice. Arch. Environ. Health 30: 538-545.

Fenters, J. D.; Bradof, J. N.; Aranyi, C.; Ketels, K.; Ehrlich, R.; Gardner, D. E. (1979) Health effects of long-term inhalation of sulfuric acid mist-carbon particle mixtures. Environ. Res. 19: 244-257.

Ferin, J.; Leach, L. J. (1977) The effects of selected air pollutants on clearance of titanic oxide particles from the lungs of rats. In: Walton, W. H.; McGovern, B., eds. Inhaled particles IV, part 1: proceedings of an international symposium organized by the British Occupational Hygiene Society; September 1975; Edinburgh, Scottland. Oxford, United Kingdom: Pergamon Press; pp. 333-341.

Fine, J. M.; Gordon, T.; Thompson, J. E.; Sheppard, D. (1987) The role of titratable acidity in acid aerosol-induced bronchoconstriction. Am. Rev. Respir. Dis. 135: 826-830.

Fish, J. E.; Menkes, H. A. (1984) Airway reactivity: role in acute and chronic disease. In: Simmons, D. H., ed. Current pulmonary, v. 5; Chicago, IL: Year Book Medical Publishers; pp. 169-199.

Gardner, D. E. (1984) Alterations in macrophage functions by environmental chemicals. EHP Environ. Health Perspect. 55: 343-358.

Gardner, D. E.; Graham, J. A. (1977) Increased pulmonary disease mediated through altered bacterial defenses. In: Sanders, C. L.; Schneider, R. P.; Dagle, G. E.; Ragan, H. A., eds. Pulmonary macrophage and epithelial cells: proceedings of the sixteenth annual Hanford Biology Symposium; September 1976; Richland, WA. Washington, DC: Technical Information Center, Energy Research and Development Administration; CONF-760927.

Gardner, D. E.; Miller, F. J.; Illing, J. W.; Kirtz, J. M. (1977) Increased infectivity with exposure to ozone and sulfuric acid. Toxicol. Lett. 1: 59-64.

Gatto, L. A. (1981) pH of mucus in rat trachea. J. Appl. Physiol. 50: 1224-1226.

Gearhart, J. M.; Schlesinger, R. B. (1986) Sulfuric acid-induced airway hyperresponsiveness. Fundam. Appl. Toxicol. 7: 681-689.

Gearhart, J. M.; Schlesinger, R. B. (1988) Response of the tracheobronchial mucociliary clearance system to repeated irritant exposure: effect of sulfuric acid mist on structure and function. Exp. Lung Res.: in press.

Godleski, J. J.; Melnicoff, M. J.; Sadri, S.; Garbeil, P. (1984) Effects of inhaled ammonium sulfate on benzo[a]pyrene carcinogenesis. J. Toxicol. Environ. Health 14: 225-238.

Goodman, R. M.; Yergin, B. M.; Landa, J. F.; Golinvaux, M. H.; Sackner, M. A. (1978) Relationship of smoking history and pulmonary function tests to tracheal mucous velocity in nonsmokers, young smokers, ex-smokers, and patients with chronic bronchitis. Am. Rev. Respir. Dis. 117: 205-214.

Grose, E. C.; Gardner, D. E.; Miller, F. J. (1980) Response of ciliated epithelium to ozone and sulfuric acid. Environ. Res. 22: 377-385.

Grose, E. C.; Richards, J. H.; Illing, J. W.; Miller, F. J.; Davies, D. W.; Graham, J. A.; Gardner, D. E. (1982) Pulmonary host defense responses to inhalation of sulfuric acid and ozone. J. Toxicol. Environ. Health 10: 351-362.

Guerrin, F.; Voisin, C.; Macquet, V.; Robin, H.; Lequien, P. (1971) Apport de la pH metric bronchique in situ [Measurement of pH in the bronchi in situ]. In: Ulmer, W. T., ed. Chronic inflammation of the bronchi: proceedings of the Societas Europaea Physiologiae Clinicae Respiratoriae and Gesellschaft fuer Lungen- und Atmungsforschung; December 1969; Bochum, Federal Republic of Germany. Basel, Switzerland: S. Karger; pp. 372-383. (Herzog, H., ed. Progress in respiration research: v. 6).

Henderson, R. F.; Gray, R. H.; Hahn, F. F. (1980a) Acute inhalation toxicity of sulfuric acid mist in the presence and absence of respirable particles. In: Diel, J. H.; Bice, D. E.; Martinez, B. S., eds. Inhalation Toxicology Research Institute Annual Report, October 1, 1979-September 30, 1980. Albuquerque, NM: Lovelace Biomedical and Environmental Research Institute; report no. LMF-84; pp. 466-469. Available from: NTIS, Springfield, VA;

Henderson, R. F.; Rebar, A. H.; DeNicola, D. B.; Henderson, T. R. (1980b) The use of pulmonary lavage fluid in screening for early indicators of lung injury. In: Sanders, C. L.; Cross, F. T.; Dagle, G. E.; Mahaffey, J. A., eds. Pulmonary toxicology of respirable particles: 19th annual Hanford life sciences symposium; October 1979; Richland, WA. Washington, DC: U. S. Department of Energy, Office of Health and Environmental Research; pp. 378-391; report no. CONF-791002. (DOE symposium series 53). Available from NTIS, Springfield, VA; CONF-791002.

Hoffman, D. J.; Campbell, K. I. (1977) Embryotoxicity of irradiated and nonirradiated catalytic converter-treated automotive exhaust. J. Toxicol. Environ. Health 3: 705-712.

Hogg, J. C.; Macklem, P. T.; Thurlbeck, W. M. (1968) Site and nature of airway obstruction in chronic obstructive lung disease. N. Engl. J. Med. 278: 1355-1360.

Holma, B. (1985) Influence of buffer capacity and pH-dependent rheological properties of respiratory mucus on health effects due to acidic pollution. Sci. Total Environ. 41: 101-123.

Holma, B.; Lindegren, M.; Andersen, J. M. (1977) pH effects on ciliomotility and morphology of respiratory mucosa. Arch. Environ. Health 32: 216-226.

Hyde, D.; Orthoefer, J.; Dungworth, D.; Tyler, W.; Carter, R.; Lum, H. (1978) Morphometric and morphologic evaluation of pulmonary lesions in beagle dogs chronically exposed to high ambient levels of air pollutants. Lab. Invest. 38: 455-469.

Jeffery, P. K.; Reid, L. M. (1977) The respiratory mucous membrane. In: Brian, J. D.; Proctor, D. F.; Reid, L. M., eds. Respiratory defense mechanism, part 1. New York, NY: Dekker; pp. 193-245.

Juhos, L. T.; Evans, M. J.; Mussenden-Harvey, R.; Furiosi, N. J.; Lapple, C. E.; Freeman, G. (1978) Limited exposure of rats to H_2SO_4 with and without O_3. J. Environ. Sci. Health C13: 33-47.

Kitabatake, M.; Imai, M.; Kasama, K.; Kobayashi, I.; Tomita, Y.; Yoshida, K. (1979) Effects of air pollutants on the experimental induction of asthma attacks in guinea pigs. Sulfuric acid mist and mixture of the mist and sulfur dioxide. Mie Med. J. 29(1): 29-36.

Kleinman, M. T.; McClure, T. R.; Mautz, W. J.; Phalen, R. F. (1985a) The interaction of ozone and atmospheric acids on the formation of lung lesions in rats. In: Lee, S. D., ed. Evaluation of the scientific basis for ozone/oxidants standards. Pittsburgh, PA: Air Pollution Control Association (TR-4); pp. 357-365.

Kleinman, M. T.; Mautz, W. J.; McClure, T. R.; Mannix, R.; Phalen, R. F. (1985b) Comparative effects of acidic and non-acidic multicomponent atmospheres on the lungs of rats exposed by inhalation. Presented at: 78th annual meeting of the Air Pollution Control Association; June; Detroit, MI. Pittsburgh, PA: Air Pollution Control Association; paper no. 85-29.3.

Kleinman, M. T.; Phalen, R. F.; Crocker, T. T.; Mautz, W. J.; Bhalla, D. K.; Mannix, R. C.; McClure, T. R. (1988) Health effects of acid aerosols formed by atmospheric mixtures. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Kwart, H.; Mosely, W. W., Jr.; Katz, M. (1963) The chemical characterization of human tracheobronchial secretion: a possible clue to the origin of fibrocystic mucus. Ann. N. Y. Acad. Sci. 106: 709-721.

Last, J. A.; Cross, C. E. (1978) A new model for health effects of air pollutants: evidence for synergistic effects of mixtures of ozone and sulfuric acid aerosols on rat lungs. J. Lab. Clin. Med. 91: 328-339.

Last, J. A.; Warren, D. L. (1987) Synergistic interaction between nitrogen dioxide and respirable aerosols of sulfuric acid or sodium chloride on rat lungs. Toxicol. Appl. Pharmacol. 90: 34-42.

Last, J. A.; Gerriets, J. E.; Hyde, D. M. (1983) Synergistic effects on rat lungs of mixtures of oxidant air pollutants (ozone or nitrogen dioxide) and respirable aerosols. Am. Rev. Respir. Dis. 128: 539-544.

Last, J. A.; Hyde, D. M.; Chang, D. P. Y. (1984) A mechanism of synergistic lung damage by ozone and a respirable aerosol. Exp. Lung Res. 7: 223-235.

Last, J. A.; Hyde, D. M.; Guth, D. J.; Warren, D. L. (1986) Synergistic interaction of ozone and respirable aerosols on rat lungs. I. Importance of aerosol acidity. Toxicology 39: 247-257.

Leikauf, G. D.; Spektor, D. M.; Albert, R. E.; Lippmann, M. (1984) Dose-dependent effects of submicrometer sulfuric acid aerosol on particle clearance from ciliated human lung airways. Am. Ind. Hyg. Assoc. J. 45: 285-292.

Lewis, T. R.; Campbell, K. I.; Vaughan, T. R., Jr. (1969) Effects on canine pulmonary function via induced NO_2 impairment, particulate interaction, and subsequent SO_x. Arch. Environ. Health 18: 596-601.

Lewis, T. R.; Moorman, W. J.; Ludmann, W. F.; Campbell, K. I. (1973) Toxicity of long-term exposure to oxides of sulfur. Arch. Environ. Health 26: 16-21.

Lewkowski, J. P.; Malanchuk, M.; Hastings, L.; Vinegar, A.; Cooper, G. P. (1979) Effects of chronic exposure of rats to automobile exhaust, H_2SO_4, SO_2, $Al_2(SO_4)_3$ and CO. In: Lee, S. D.; Mudd, J. B., eds. Assessing toxic effects of environmental pollutants. Ann Arbor, MI: Ann Arbor Science Publishers, Inc.; pp. 187-217.

Lippmann, M. (1985) Airborne acidity: estimates of exposure and human health effects. EHP Environ. Health Perspect. 63: 63-70.

Lippmann, M.; Schlesinger, R. B.; Leikauf, G.; Spektor, D.; Albert, R. E. (1982) Effects of sulphuric acid aerosols on respiratory tract airways. In: Walton, W. H., ed. Inhaled particles V: proceedings of an international symposium organized by the British Occupational Hygiene Association; September 1980; Cardiff, United Kingdom; Ann. Occup. Hyg. 26: 677-690.

Loscutoff, S. M.; Cannon, W. C.; Buschbom, R. L.; Busch, R. H.; Killand, B. W. (1985) Pulmonary function in elastase-treated guinea pigs and rats exposed to ammonium sulfate or ammonium nitrate aerosols. Environ. Res. 36: 170-180.

Mannix, R. C.; Phalen, R. F.; Kenoyer, J. L.; Crocker, T. T. (1982) Effect of sulfur dioxide-sulfate exposure on rat respiratory tract clearance. Am. Ind. Hyg. Assoc. J. 43: 679-685.

Matijak-Schaper, M.; Wong, K.-L.; Alarie, Y. (1983) A method to rapidly evaluate the acute pulmonary effects of aerosols in unanesthetized guinea pigs. Toxicol. Appl. Pharmacol. 69: 451-460.

Matsuba, K.; Thurlbeck, W. M. (1973) Disease of the small airways in chronic bronchitis. Am. Rev. Respir. Dis. 107: 552-558.

Matsumura, Y. (1970) The effects of ozone, nitrogen dioxide, and sulfur dioxide on the experimentally induced allergic respiratory disorder in guinea pigs. I. The effect on sensitization with albumin through the airway. Am. Rev. Respir. Dis. 102: 430-437.

Mautz, W. J.; Bufalino, C.; Kleinman, M. T.; Lejnieks, R. M.; Phalen, R. F. (1985) Pulmonary function of exercising dogs exposed to ozone alone or in combination with SO2 and acid aerosol. Presented at: 78th annual meeting of the Air Pollution Control Association; June; Detroit, MI. Pittsburgh, PA: Air Pollution Control Association; paper no. 85-29.4.

Moore, P. F.; Schwartz, L. W. (1981) Morphological effects of prolonged exposure to ozone and sulfuric acid aerosol on the rat lung. Exp. Mol. Pathol. 35: 108-123.

Mossberg, B.; Camner, P. (1980) Impaired mucociliary transport as a pathogenetic factor in obstructive pulmonary diseases. Chest 77(suppl.): 265-266.

Murray, F. J.; Schwetz, B. A.; Nitschke, K. D.; Crawford, A. A.; Quast, J. F.; Staples, R. E. (1979) Embryotoxicity of inhaled sulfuric acid aerosol in mice and rabbits. J. Environ. Sci. Health C13: 251-266.

Nathanson, I.; Nadel, J. A. (1984) Movement of electrolytes and fluid across airways. Lung 162: 125-137.

Naumann, B. D.; Schlesinger, R. B. (1986) Assessment of early alveolar particle clearance and macrophage function following an acute inhalation of sulfuric acid mist. Exp. Lung Res. 11: 13-33.

Niederman, M. S.; Rafferty, T. D.; Sasaki, C. T.; Merrill, W. W.; Matthay, R. A.; Reynolds, H. Y. (1983) Comparison of bacterial adherence to ciliated and squamous epithelial cells obtained from the human respiratory tract. Am. Rev. Respir. Dis. 127: 85-90.

Osebold, J. W.; Gershwin, L. J.; Zee, Y. C. (1980) Studies on the enhancement of allergic lung sensitization by inhalation of ozone and sulfuric acid aerosol. J. Environ. Pathol. Toxicol. 3: 221-234.

Pattle, R. E.; Cullumbine, H. (1956) Toxicity of some atmospheric pollutants. Br. Med. J. 2: 913-916.

Pattle, R. E.; Burgess, F.; Cullumbine, H. (1956) The effects of a cold environment and of ammonia on the toxicity of sulphuric acid mist to guinea-pigs. J. Pathol. Bacteriol. 72: 219-232.

Pepelko, W. E.; Mattox, J. K.; Cohen, A. L. (1980) Toxicology of ammonium sulfate in the lung. Bull. Environ. Contam. Toxicol. 24: 156-160.

Petty, T. L.; Silvers, G. W.; Stanford, R. E. (1983) The morphology and morphometry of small airways disease (relevance to chronic obstructive pulmonary disease). Trans. Clin. Climatol. Assoc. 94: 130-140.

Phalen, R. F.; Kenoyer, J. L.; Crocker, T. T.; McClure, T. R. (1980) Effects of sulfate aerosols in combination with ozone on elimination of tracer particles inhaled by rats. J. Toxicol. Environ. Health 6: 797-810.

Phipps, R. J. (1981) The airway mucociliary system. In: Widdicombe, J. G., ed. International review of physiology. Respiratory physiology III, v. 23. Baltimore, MA: University Park Press; pp. 213-260.

Pinto, M.; Birnbaum, S. C.; Kadar, T.; Goldberg, G. M. (1979) Lung injury in mice induced by factors acting synergistically with inhaled particulate antigen. Clin. Immunol. Immunopathol. 13: 361-368.

Popa, V.; Douglas, J. S.; Bouhuys, A. (1974) Airway responses to histamine, acetylcholine, and antigen in sensitized guinea pigs. J. Lab. Clin. Med. 84: 225-234.

Proctor, D. F. (1979) Tests of airway defense mechanisms. In: Macklem, P. T.; Permutt, S., eds. The lung in the transition between health and disease. New York, NY: Marcel Dekker, Inc.; pp. 227-241.

Puchelle, E.; Zahm, J. M. (1984) Influence of rheological properties of human bronchial secretions on the ciliary beat frequency. Biorheology 21: 265-272.

Ramsdale, E. H.; Roberts, R. S.; Morris, M. M.; Hargreave, F. E. (1985) Differences in responsiveness to hyperventilation and methacholine in asthma and chronic bronchitis. Thorax 40: 422-426.

Ramsdell, J. W.; Nachtwey, F. J.; Moser, K. M. (1982) Bronchial hyperreactivity in chronic obstructive bronchitis. Am. Rev. Respir. Dis. 126: 829-832.

Reid, L.; Jones, R. (1979) Bronchial mucosal cells. Fed. Proc. Fed. Am. Soc. Exp. Biol. 38: 191-196.

Reid, L.; Bhaskar, K.; Coles, S. (1983) Control and modulation of airway epithelial cells and their secretions. Exp. Lung Res. 4: 157-170.

Sackner, M. A.; Ford, D.; Fernandez, R.; Cipley, J.; Perez, D.; Kwoka, M.; Reinhart, M.; Michaelson, E. D.; Schreck, R.; Wanner, A. (1978) Effects of sulfuric acid aerosol on cardiopulmonary function of dogs, sheep, and humans. Am. Rev. Respir. Dis. 118: 497-510.

Sackner, M. A.; Dougherty, R. L.; Chapman, G. A.; Cipley, J.; Perez, D.; Kwoka, M.; Reinhart, M.; Brito, M.; Schreck, R. (1981) Effects of brief and intermediate exposures to sulfate submicron aerosols and sulfate injections on cardiopulmonary function of dogs and tracheal mucous velocity of sheep. J. Toxicol. Environ. Health 7: 951-972.

Schaper, M.; Alarie, Y. (1985) The effects of aerosols of carbamylcholine, serotonin and propranolol on the ventilatory response to CO_2 in guinea pigs and comparison with the effects of histamine and sulfuric acid. Acta Pharmacol. Toxicol. 56: 244-249.

Schaper, M.; Kegerize, J.; Alarie, Y. (1984) Evaluation of concentration-response relationships for histamine and sulfuric acid aerosols in unanesthetized guinea pigs for their effects on ventilatory response to CO_2. Toxicol. Appl. Pharmacol. 73: 533-542.

Schiff, L. J.; Bryne, M. M.; Fenters, J. D.; Graham, J. A.; Gardner, D. E. (1979) Cytotoxic effects of sulfuric acid mist, carbon particulates, and their mixtures on hamster tracheal epithelium. Environ. Res. 19: 339-354.

Schlesinger, R. B. (1984) Comparative irritant potency of inhaled sulfate aerosols - effects on bronchial mucociliary clearance. Environ. Res. 34: 268-279.

Schlesinger, R. B. (1985) Comparative deposition of inhaled aerosols in experimental animals and humans: a review. J. Toxicol. Environ. Health 15: 197-214.

Schlesinger, R. B. (1987) Functional assessment of rabbit alveolar macrophages following intermittent inhalation exposures to sulfuric acid mist. Fundam. Appl. Toxicol. 8: 328-334.

Schlesinger, R. B. (1988) Factors affecting the response of lung clearance systems to acid aerosols: the role of exposure concentration, exposure time, and relative acidity. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Schlesinger, R. B.; Gearhart, J. M. (1986) Early alveolar clearance in rabbits intermittently exposed to sulfuric acid mist. J. Toxicol. Environ. Health 17: 213-220.

Schlesinger, R. B.; Gearhart, J. M. (1987) Intermittent exposures to mixed atmospheres of nitrogen dioxide and sulfuric acid: effect on particle clearance from the respiratory region of rabbit lung. Toxicology 44: 309-319.

Schlesinger, R. B.; Lippmann, M.; Albert, R. E. (1978) Effects of short-term exposures to sulfuric acid and ammonium sulfate aerosols upon bronchial airway function in the donkey. Am. Ind. Hyg. Assoc. J. 39: 275-286.

Schlesinger, R. B.; Halpern, M.; Albert, R. E.; Lippmann, M. (1979) Effect of chronic inhalation of sulfuric acid mist upon mucociliary clearance from the lungs of donkeys. J. Environ. Pathol. Toxicol. 2: 1351-1367.

Schlesinger, R. B.; Naumann, B. D.; Chen, L. C. (1983) Physiological and histological alterations in the bronchial mucociliary clearance system of rabbits following intermittent oral or nasal inhalation of sulfuric acid mist. J. Toxicol. Environ. Health 12: 441-465.

Schlesinger, R. B.; Chen, L.-C.; Driscoll, K. E. (1984) Exposure-response relationship of bronchial mucociliary clearance in rabbits following acute inhalations of sulfuric acid mist. Toxicol. Lett. 22: 249-254.

Schwartz, L. W.; Moore, P. F.; Chang, D. P.; Tarkington, B. K.; Dungworth, D. L.; Tyler, W. S. (1977) Short-term effects of sulfuric acid aerosols on the respiratory tract. A morphological study in guinea pigs, mice, rats and monkeys. In: Lee, S. D., ed. Biochemical effects of environmental pollutants. Ann Arbor, MI: Ann Arbor Science Publishers, Inc.; pp. 257-271.

Schwartz, L. W.; Zee, Y. C.; Tarkington, B. K.; Moore, P. F.; Osebold, J. W. (1979) Pulmonary responses to sulfuric acid aerosols. In: Lee, S. D.; Mudd, J. B., eds. Assessing toxic effects of environmental pollutants. Ann Arbor, MI: Ann Arbor Science Publishers, Inc.; pp. 173-186.

Silbaugh, S. A.; Mauderly, J. L. (1986) Effects of ozone and sulfuric acid aerosol on gas trapping in the guinea pig lung. J. Toxicol. Environ. Health 18: 133-141.

Silbaugh, S. A.; Mauderly, J. L.; Macken, C. A. (1981a) Effects of sulfuric acid and nitrogen dioxide on airway responsiveness of the guinea pig. J. Toxicol. Environ. Health 8: 31-45.

Silbaugh, S. A.; Wolff, R. K.; Johnson, W. K.; Mauderly, J. L.; Macken, C. A. (1981b) Effects of sulfuric acid aerosols on the pulmonary function of guinea pigs. J. Toxicol. Environ. Health 7: 339-352.

Simonsson, B. G. (1965) Clinical and physiological studies on chronic bronchitis. III. Bronchial reactivity to inhaled acetylcholine. Acta Allergologica 20: 325-348.

Stara, J. F.; Dungworth, D. L.; Orthoefer, J. G.; Tyler, W. S., eds. (1980) Long-term effects of air pollutants: in canine species. Cincinnati, OH: U. S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-80-014. Available from: NTIS, Springfield, VA; PB81-144875.

Stutts, M. J.; Boucher, R. C.; Bromberg, P. A.; Gatzy, J. T. (1981) Effects of ammonium and nitrate salts on ion transport across the excised canine trachea. Toxicol. Appl. Pharmacol. 60: 91-105.

Thomas, M. D.; Hendricks, R. H.; Gunn, F. D.; Critchlow, J. (1958) Prolonged exposure of guinea pigs to sulfuric acid aerosol. Arch. Ind. Health 17: 70-80.

Treon, J. F.; Dutra, F. R.; Cappel, J.; Sigmon, H.; Younker, W. (1950) Toxicity of sulfuric acid mist. AMA Arch. Ind. Hyg. Occup. Med. 2: 716-734.

Utell, M. J.; Morrow, P. E.; Hyde, R. W. (1982) Comparison of normal and asthmatic subjects' responses to sulphate pollutant aerosols. In: Walton, W. H., ed. Inhaled particles V: proceedings of an international symposium organized by the British Occupational Hygiene Association; September 1980; Cardiff, United Kingdom; Ann. Occup. Hyg. 26: 691-697.

Warren, D. L.; Last, J. A. (1987) Synergistic interaction of ozone and respirable aerosols on rat lungs: III. ozone and sulfuric acid aerosol. Toxicol. Appl. Pharmacol. 88: 203-216.

Warren, D. L.; Guth, D. J.; Last, J. A. (1986) Synergistic interaction of ozone and respirable aerosols on rat lungs. II. Synergy between ammonium sulfate aerosol and various concentrations of ozone. Toxicol. Appl. Pharmacol. 84: 470-479.

Wolff, R. K. (1986) Effects of airborne pollutants on mucociliary clearance. EHP Environ. Health Perspect. 66: 223-237.

Wolff, R. K.; Silbaugh, S. A.; Brownstein, D. G.; Carpenter,R. L.; Mauderly, J. L. (1979) Toxicity of 0.4- and 0.8-μm sulfuric acid aerosols in the guinea pig. J. Toxicol. Environ. Health 5: 1037-1047.

Wolff, R. K.; Henderson, R. F.; Dahl, A. R.; Felicetti, S. A.; Gray, R. H. (1980) Effects of H_2SO_4 on tracheal mucus clearance. In: Sanders, C. L.; Cross, F. T.; Dagle, G. E.; Mahaffey, J. A., eds. Pulmonary toxicology of respirable particles: 19th annual Hanford life sciences symposium; October 1979; Richland, WA. Washington, DC: U. S. Department of Energy, Office of Health and Environmental Research; pp. 378-391; Available from: NTIS, Springfield, VA; CONF-791002. (DOE symposium series 53).

Wolff, R. K.; Muggenburg, B. A.; Silbaugh, S. A. (1981) Effect of 0.3 and 0.9 μm sulfuric acid aerosols on tracheal mucous clearance in beagle dogs. Am. Rev. Respir. Dis. 123: 291-294.

Wolff, R. K.; Henderson, R. F.; Gray, R. H.; Carpenter, R. L.; Hahn, F. F. (1986) Effects of sulfuric acid mist inhalation on mucous clearance and on airway fluids of rats and guinea pigs. J. Toxicol. Environ. Health 17: 129-142.

Wong, K. L.; Alarie, Y. (1982) A method for repeated evaluation of pulmonary performance in unanesthetized, unrestrained guinea pigs and its application to detect effects of sulfuric acid mist inhalation. Toxicol. Appl. Pharmacol. 63: 72-90.

5. CONTROLLED HUMAN EXPOSURE STUDIES OF ACID AEROSOLS

5.1 INTRODUCTION

The effects of inhaled acid aerosols were studied initially because of interest in occupational exposures. These early studies, conducted in the 1950's, have been followed by an extensive series of investigations, most of which have been completed since 1977. The impetus for the more recent studies appears to have been the concern over production of sulfates by automotive catalytic converters. The sparse data on environmental levels of airborne acidity have hindered the design of human exposure studies. The majority of studies have been conducted using sulfuric acid aerosol and its salts, although the effects of nitrates and hydrochloric acid aerosols have also been examined. A broad range of concentrations of these aerosols have been studied ranging from 10 $\mu g/m^3$ to more than 1,000 $\mu g/m^3$. The "dose" of inhaled aerosol has been varied by using exposures of different durations (from 10 minutes up to 4 hours) or by increasing the ventilatory exchange by incorporating exercise. In addition to these rather straightforward considerations, the delivered "dose" is also affected by the upper airway path traversed by the aerosol and the size of the particles as well as their potential for hygroscopic growth in the respiratory tract, as discussed in Chapter 3.

The studies reported in this section have been conducted on both normal and asthmatic subjects; the latter group represents a potentially "susceptible" population. Aerosols have been inhaled either directly through a mouthpiece or facemask or during unencumbered breathing in an environmental chamber. Several different types of measurements have been made following exposure. In most cases, some measures of lung function such as spirometry or plethysmography have been made. In addition, the effects of acid aerosols on airway reactivity and on mucociliary clearance have been studied rather extensively. Another area of investigation has been the influence of aerosol acidity and the potential for neutralization of acid by ammonia or by airway surface fluid buffers.

The first investigation into the effects of acid aerosols on human lung function was conducted by Amdur and co-workers in 1952 (Amdur et al., 1953). Using a group of 15 subjects, they studied the retention of inhaled sulfuric acid aerosol, the changes in respiratory pattern induced by the acid aerosol, and the sensory threshold for olfactory detection of sulfuric acid mist.

The aerosol was generated from fuming H_2SO_4; the particle size was reported to be 1 μm. Calculated respiratory tract aerosol particle retention averaged 77 percent and ranged from 50 percent to 87 percent in the exposure concentration range of 0.4 to 1.0 mg/m^3. Aerosol concentrations of less than 1 mg/m^3 could not be detected by either odor or taste and apparently caused no irritation. All subjects were able to detect a concentration of 3 mg/m^3. At 5 mg/m^3, a deep breath usually produced coughing.

Changes in respiratory pattern were reported at 0.35 to 0.50 mg/m^3 sulfuric acid aerosol (SAA). A reduction in both maximum inspiratory (-15 percent) and expiratory (-20 percent) flow was accompanied by a modest tachypnea (+35 percent increase in respiratory frequency) and a decrease (-28 percent) in tidal volume. These findings were interpreted as a typical response to respiratory irritants. This study did not, unfortunately, generate the necessary interest at the time for a large number of subsequent investigations of the effects of acid aerosol exposure in man.

One subsequent study, conducted by Sim and Pattle (1957), reported the responses to relatively high concentrations of large-particle sulfuric acid aerosols. Because of the high concentrations used and the somewhat uncontrolled nature of the exposures, this study provided little useful information.

The next reported study of human exposure to sulfuric acid aerosol was that of Larson et al. (1977). This paper reported the first evidence that oral ammonia could effectively neutralize a portion of the inhaled acid aerosol; it is discussed in more detail in Chapter 3. Although interest in sulfuric acid aerosol as an air contaminant dates back to the "fog" episodes, virtually all of the studies that address human health effects, which are relevant to ambient exposures, have been published since 1977. This important study served as a lead-in to a number of subsequent studies of the effects of acid aerosols.

The studies described in this section deal with human experimental exposures to inhaled acids and their salts; such studies are frequently referred to as human "clinical" studies. The methods used in these studies are similar to those used in experimental studies of criteria pollutants such as ozone, NO_2, and SO_2. A detailed discussion of the methodology is beyond the scope of the chapter but some points may be important in evaluating the studies discussed subsequently.

Inhaled substances may be breathed directly through a mouthpiece or from air within an environmental chamber or a facemask. One of the major considerations is that air breathed orally bypasses the nose, which may remove soluble pollutants from the air as well as humidify the incoming air. On the other hand, air breathed nasally encounters greater flow resistance and bypasses a potential source of ammonia in the mouth. The volume of air exchanged is a function of the metabolic rate or level of activity of the exposed individual; exercising subjects will therefore inhale more of the pollutant gas or aerosol. The temperature and humidity of the inspired air may be an important factor, especially for asthmatics. Of course, the duration of the exposure and the concentration of pollutant are essential in quantitating the exposure.

5.2 PULMONARY FUNCTION EFFECTS OF H_2SO_4 IN NORMAL SUBJECTS

The effects of sulfuric acid aerosol have been studied extensively in healthy subjects without history of respiratory disease. Such subjects are typically young adult males whose atopic status has usually not been determined. Studies completed since 1978 include exposures to a range of concentrations from 75 to 1,500 $\mu g/m^3$ with a variety of aerosol particle sizes from 0.1 to 1.5 µm. This section includes only the data from "normal" subjects. If data on asthmatics or other types of subjects were also included in a report, these data are discussed separately in the appropriate subsection (Section 5.6). Many of the details of the experimental procedures are presented in the tables to avoid a cumbersome text.

Newhouse et al. (1978) exposed 10 subjects to 1,000 $\mu g/m^3$ sulfuric acid aerosol (0.5 µm) under temperate (22°C), humid (70 percent RH) conditions for a period of 2 h. The exposure period included a total of 20 min of heavy exercise (70 to 75 percent of maximal aerobic power); oral breathing was obligatory throughout exposure. There were no significant changes in VC, $FEV_{1.0}$, or MMFR as a result of this exposure.

Sackner et al. (1978) reported the results of a series of exposures of both normal and asthmatic humans to sulfuric acid aerosol concentrations ranging from 10 to 1,000 $\mu g/m^3$. These studies involved a total of 17 normal subjects of mixed age and gender and were performed with oral breathing at rest. There were no significant effects of up to 1,000 $\mu g/m^3$ sulfuric acid aerosol of any of the extensive series of tests of lung function performed after exposure in these subjects.

Six subjects exposed to 75 $\mu g/m^3$ sulfuric acid aerosol were studied by Avol and associates (1979). Exposures included light intermittent exercise and lasted for 2 h. There were no significant respiratory function effects of this exposure in these subjects.

In a study primarily designed to examine the effects of sulfuric acid aerosol on mucociliary clearance, Leikauf et al. (1981) exposed 10 healthy nonsmokers for one hour to 110, 330, and 980 $\mu g/m^3$ of 0.5 μm sulfuric acid aerosol via nasal mask. There were no significant effects of H_2SO_4 exposure on airway resistance, partial maximum expiratory flow at 25 percent of vital capacity (V_{25}; partial expiratory flow-volume test), or on an index of distribution of ventilation based on multiple breath nitrogen washout.

Kerr et al. (1981) examined the effects of a longer exposure to 100 $\mu g/m^3$ sulfuric acid (0.1 to 0.3 μm). Two groups of 14 subjects each, one consisting of smokers (11 M, 3 F) and the other of nonsmokers (8 M, 6 F) were exposed for 4 hr in an environmental chamber; moderate exercise was performed for two 15-min periods during exposure. There were no significant alterations in lung function (forced expiratory tests, single breath nitrogen washout, airway resistance, or pulmonary compliance).

In a study using a similar protocol, Horstman et al. (1982) confirmed the absence of significant change in pulmonary function following exposure to low sulfuric acid aerosol levels (108 $\mu g/m^3$ of 0.5 μm aerosol). A control group of 17 and an experimental group of 18 male subjects were exposed on two consecutive days for 4 h including two 15-min periods of moderately heavy exercise. Each group received a clean air exposure on the first day. On the second exposure day, the control group received clean air and the experimental group received H_2SO_4. The exposure had no effect on breathing pattern, spirometry, or airway resistance.

Horvath et al. (1982) exposed 11 male subjects to clean air and to 233, 418, and 939 $\mu g/m^3$ of 0.9 μm sulfuric acid aerosol. Exposures lasted 2 hr and included four 15-min periods of mild intermittent exercise. A small decrease (101 mL; -2.1 percent) in $FEV_{1.0}$ was reported for the 939 µg/m^3 exposure. Since this change was similar in relative magnitude to other spirometry measurements in the study, it is quite possible that the "significance" of this result occurred by chance (i.e., a total of 12 measurements were tested for significance at the $P < 0.05$ level, which increases the likelihood of finding a "significant" response by chance alone). Although there was no convincing evidence of pulmonary function effects, symptoms of cough and dry or irritated throat were more prevalent at the highest (939 µg/m^3) concentration and were noted mainly at the beginning of the exposure period. The occurrence of significant symptoms suggests that the significance of the small change in $FEV_{1.0}$ reported at the 939 µg/m^3 concentration could be real. However, Avol et al. (1986) noted increased symptoms, in the absence of changes in spirometry at both 1,000 and 2,000 µg/m^3 of H_2SO_4 "acid fog" aerosol.

Utell et al. (1982) exposed normal volunteers to 100 and 1,000 µg/m^3 of 0.5 to 1.0 µm "dry" sulfuric acid aerosol for 16 min via mouthpiece breathing. This resting exposure produced no significant effect on airway conductance yet induced "quite small" but significant changes (magnitude not reported) in maximum expiratory flow on maximum expiratory flow volume curves (MEF60%TLC) and partial expiratory flow volume curves (PMEF60%TLC, PMEF40%TLC) after the 1,000 µg/m^3 exposure.

From a comprehensive exposure study including several pollutants, Stacy et al. (1983) reported results for 11 subjects exposed to 100 µg/m^3 sulfuric acid aerosol. The 4-h exposure, which included 30 min of moderate exercise, produced no significant effects on pulmonary function.

Utell et al. (1984) reported results of a study in which 14 normal subjects were exposed to 100 and 1,000 µg/m^3 sulfuric acid aerosol for 16 min; there were no effects on SGaw, $FEV_{1.0}$, or V60%TLC.

During a study examining the effects of ozone plus H_2SO_4, Horvath et al. (1987) exposed 9 men to a range of 1,200 to 1,600 µg/m^3 sulfuric acid aerosol for 2 h. In contrast to their previous study (Horvath et al., 1982), an extremely fine aerosol (<0.1 µm) was used. The exposures were conducted under warm, humid conditions and included a total of 60 min of moderate intermittent exercise. There were no significant changes in FVC, $FEV_{1.0}$, $FEF_{25-75\%}$ or Raw attributable to sulfuric acid aerosol exposure. Although evaluation of subject symptoms was apparently conducted, the symptom results were not included in their report.

Avol et al. (1986) have exposed subjects to 0, 500, 1,000, and 2,000 μg/m^3 of acid fog (see details in 5.6 or Table 5-1). In the healthy normal subjects, there was no indication of pulmonary function effects after any of the exposures. However, upper and lower respiratory symptoms increased after all exposures but most notably after the 2,000 μg/m^3 exposure. Airway reactivity to methacholine was unchanged after the exposures.

The results of the above 11 studies, which investigated the effects of sulfuric acid aerosols over a broad range of particle sizes (0.1 to 10 μm) and under a variety of exposure conditions (duration, temperature, humidity, inhalation route, activity level), consistently demonstrated that there were no pulmonary function effects of up to 500 μg/m^3 sulfuric acid aerosol for durations up to 4 hr. Although there is some suggestion that pulmonary function effects may begin at concentrations of approximately 1,000 μg/m^3, the demonstration of responses is confined to only a few of many studies and the effects were very small in magnitude and not consistently demonstrated across a variety of exposure conditions. However, symptoms of upper respiratory discomfort were reported after exposure to 1,000 μg/m^3 in two studies of normal subjects.

5.3 EFFECTS OF ACID AEROSOLS ON BLOOD BIOCHEMISTRY

Chaney and co-workers (1980a) examined the effects of sulfuric acid aerosol exposure on blood biochemical markers. Twenty subjects were exposed to 100 μg/m^3 of 0.5 μm sulfuric acid aerosol for 4 h at rest on two consecutive days. Blood samples were taken immediately before and after exposure, and then again one day after exposure. There was no effect of acid aerosol exposure on any of the measured blood parameters: glutathione, red blood cell (RBC) glutathione reductase, RBC glucose-6-phosphate dehydrogenase, lysozyme, SGOT (serum glutamic-oxaloacetic transaminase), serum vitamin E, and 2,3-diphosphoglycerate (DPG).

The above study was repeated (Chaney et al., 1980b) using a slightly modified experimental design and an exposure protocol that incorporated exercise. (The exercise protocol is identical to that described in Section 5.2 for Horstman et al., 1982). The blood parameters measured were the same as in the resting study except that G6PD was omitted. This study demonstrated no effects of sulfuric acid aerosol exposure on these human blood biochemical markers.

TABLE 5-1. SUMMARY OF CONTROLLED HUMAN EXPOSURE STUDIES OF ACID AEROSOLS

Reference	Aerosol	Concentration $\mu g/m^3$	MMAD	GSD	N	Subj Char	Exposure Duration	$\dot{V}_E$	Temp°C	RH	SPIR	PLETH	Symptom & Other
Amdur et al. (1953)	H_2SO_4	400-5000	1.0	--	15	Normal	--	Rest	--	--	--	--	Rf ↑ 35% TV - 28%
Avol et al. (1979)	$(NH_4)_2SO_4$	117-325	0.3-0.6	3	6	Normal, Asthmatic	2h IE	2X	31	40/85	NC	--	SBN2 - NC
	NH_4HSO_4	46-47	0.5-0.6	3	6	"	2h IE	2X	31	40	NC	--	RT - NC
	H_2SO_4	93-111	0.5-0.6	3	6	"	2h IE	2X	31	40	NC	--	
Avol, Linn, Hackney (1986)	Acid Fog H_2SO_4	0 500 1000 2000	10 Acid Fog (VMD)		22	Normal	1h	46				NC	NC Increased symptoms after exposure in both groups. NC in methacholine reactivity
					22	Asthmatic	1h E	41	10°	100			
Balmes et al. (1987)	Hypo-osmolar +H_2SO_4 +HNO_3 Isso-osmolar H_2SO_4	--	5.2 6.3	--	12	Asthmatics M, F	VAR	Rest	--	--	--	See text of Chapter 3	
Chaney et al. (1980a)	H_2SO_4	100	0.5	--	17, 20	M, NS	4h	Rest	20	40	--	--	No effects on blood enzymes, etc.
Chaney et al. (1980b)	H_2SO_4				18, 17	M, NS	4h, IE	2-15 min Exercise	22	40	--	--	No effects on blood enzymes, etc.
Fine et al. (1987)	H_2SO_4 Unbuffered HCl Unbuffered H_2SO_4 Buffered HCl Buffered	~10,000	5.3 -6.2	1.7	8	Asthmatic Nonsmokers	3 min	Rest Mouthpiece 11 L/min	--	--	--	NC NC SRaw increased ~50% SRaw increased ~50%	Cough Suggest Broncho-constriction related to aerosol titratable acidity
Hackney et al. (1988)	H_2SO_4	500 950 1500	0.9	--	20	Asthmatics	1h, IE	50	21	50	--	FEV_1 - 10% at 950, 1,500	↑ Symptoms

(continued on the following page)

TABLE 5-1. (continued)

Reference	Aerosol	Concen-tration μg/m³	MMAD	GSD	N	Subj Char	Exposure Duration	$\dot{V}_E$	Temp°C	RH	SPIR	PLETH	Symptom & Other	
Horstman et al. (1982)	H_2SO_4	100	0.5	--	17, 18	M, NS	4h, IE	Est. 6X	22	39	NC	NC	NC	
Horvath et al. (1982)	H_2SO_4	223 418 939	0.92	1.7	11	Normal Male NS	2h, IE	30 L/min	22	55	NC NC FEV 1.0 - 2%	NC NC NC	NC NC Throat irritation cough	
Horvath et al. (1987)	H_2SO_4	1200-1600	0.05	--	9	Normal M, NS	2h, IE	33 L/min	35	83	NC	NC	--	
Kerr et al. (1981)	H_2SO_4	100	0.1-0.3	--	28	Normal M, F	4h	8.5 L/min	22	60	NC	NC	NC	
Kleinman et al. (1980)	NH_4NO_3	200	1.1	3.3	20	Normal M, F	2h, IE	2X	31	40	NC	NC	NC	
Kleinman et al. (1981a)	H_2SO_4, O_3, SO_2	103	0.5	3	19	Normal	2h, IE	2X	31	40	FEV 1.0 - 3.7%		Increased Total Symptoms	RT-NC
Kleinman et al. (1981b)	$FE_2(SO_4)_3$	75	2.0	3	20 18	Normal Asthmatic	2h, IE 2h, IE	Est. 2X Est. 2X	31 31	40 40	NC NC	NC NC	NC NC	
Kleinman et al. (1985)	$ZnNH_4SO_4$ + NO_2 SO_2	26 μg 0.5 (ppm) 0.5 (ppm)	1.0-1.3	3	20	Normal, NS, M, F	2.25h, IE	2X	20	85	NC	NC	NC	
Koenig et al. (1983)	H_2SO_4 +NaCl	110	0.6	1.5	10	Asthmatic Adolescent M, F Daily BD	30 min rest 10 min EX	39-40	22	75	$FEV_{1.0}$ -8% $\dot{V}_{50}$ -21%	--	NC	RT + 40%
Koenig et al. (1987)	H_2SO_4 H_2SO_4 + SO_2	68 0.1 ppm	0.55	1.5	9	Asthmatic Adolescent	30 min rest 10 min EX	32	25	65	$FEV_{1.0}$ -6% $FEV_{1.0}$ -4%	--		RT + 12% RT + 15% NC in symptom

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TABLE 5-1. (continued)

Reference	Aerosol	Concentration µg/m³	MMAD	GSD	N	Subj Char	Exposure Duration	$\dot{V}_E$	Temp°C	RH	SPIR	PLETH	Symptom & Other	
Koenig et al. (1985)	H_2SO_4	103	0.6	1.5	10	Adolescent Asthmatic Daily BD	30 min rest 20 min EX	43-mask	22	75	$FEV_{1.0}$-8% $\dot{V}_{50}$-16%	--	RT + 35%	
								43-mouthpiece			$FEV_{1.0}$-7% $\dot{V}_{50}$-22%	--	RT + 45%	
Kulle et al. (1982)	H_2SO_4	100	0.13	2.4	12	Normal NS	3.75h rest 0.25h EX	Est. 30-35	22	60	NC	NC	NC	Possible decrease in bronchial reactivity to methacholine
Kulle et al. (1984)	$(NH_4)_2SO_4$	528	0.97	1.6	10 M 10 F	Normal NS	4h, IE 2-15 min EX	Est. 30-35	22	60	NC	NC	NC	Suggested eye irritation
Larson et al. (1977)	H_2SO_4	--	--	--	--	--	--	--	--	--			Demonstrated possible neutralization of H_2SO_4 by oral ammonia	
Leikauf et al. (1981)	H_2SO_4 (7.5 µm) (FE_2O_3)	110	0.5	1.9	10	Normal	1h rest	Nasal	26	46	NC	NC	Mucociliary clearance faster	
		330									NC	NC	No net effect	
		980									NC	NC	Mucociliary clearance slowed	
Linn et al. (1981)	$ZnSO_4$ $(NH_4)_2SO_4$ with NaCl	16	1.1	2.6	21	Normal M, F	2h, IE	Est. 25	20	85	NC	NC	NC	
		(300)			19	Asthmatic M, F					NC NC	NC NC	NC NC	
Linn et al. (1986)	H_2SO_4 + other sulfates	122 242 410	0.6	2.6	27	Asthmatic Allergic Some BD	1h, IE	42	22	60	NC NC NC	NC NC NC	No change in cold air reactivity	
Linn et al. (1986) (ABST)	H_2SO_4 Acid Fog	150	--	--	6	Normal	60 min IE	EST 50	--	--	NC			No change methacholine reactivity
		150	--	--	6	Asthmatic					NC			
		680			6	Normal					NC		Symptoms, cough increased	
		680			6	Asthmatic					NC	SGaw increased	Symptoms, cough increased	

(continued on the following page)

TABLE 5-1. (continued)

Reference	Aerosol	Concen-tration µg/m³	MMAD	GSD	N	Subj Char	Exposure Duration	$\dot{V}_E$	Temp°C	RH	SPIR	PLETH	Symptom & Other
Newhouse et al. (1978)	H_2SO_4 + SO_2	1000 (5 ppm)	0.5	2.6	10	Normal NS	30 min rest 20 min EX	Est. 60	22	70	--	NC (MMFR-8%)	Increased clearance from large airways
Sackner et al. (1978)	H_2SO_4	10 100 1000	0.1-0.2	--	5 normal 5 severe Asthmatics		10 min rest		--	20-30	NC	NC	RT-NC No delayed effects on asthmatics
		1000	0.1-0.2	--	6 normal 6 severe Asthmatics		10 min rest		--	--	NC	NC	RT-NC
		1000	0.1-0.2		6 normal 6 Asthmatic		10 min rest		--	--	NC	NC	RT-NC
Sackner et al. (1979)	$NaNO_3$	10 100 1000 1000	0.1	--	5 normals 5 Asympto-matic Asthmatics 12 Normals 12 Asth-matics		10 min Rest Mouthpiece		-- --	-- --	Normals possible decrease in $\dot{V}_{50VC}$ no effects in asth-matics	Possible decrease in SGaw	No symptoms, no other cardio-pulmonary responses
Spektor et al. (1985)	H_2SO_4	110 319 971	0.5	1.9	10	Asthmatic M, F Mild-severe	1h	Rest Nasal	27	47	$FEV_{1.0}$-5% MMEF-6%	SGaw-6%	Mucociliary clearance Decreased 50%
Spektor et al. (1988)	H_2SO_4	100	0.5	1.9	10	Normal	60 min 120 min	Rest Normal	27	47	NC	NC	Clearance ↓ 50% at 1 hr ↓ 62% at 2 hr
Sim and Pattle (1957)	H_2SO_4	300-3900	1.0 1.5	-- --	316 exp. 40 exp.	Normal	30-60 min	Rest	18 24.5	62 91	--	--	↑35-100% Resistance +43-150% Resistance cough, lacrimation
Stacy et al. (1983)	H_2SO_4 $(NH_4)_2SO_4$ NH_4HSO_4 NH_4NO_3	~100 ~100 ~100 ~100	0.55	1.6	10 10 10 10	Normal M, NS	4h IE 2X 15 min EX	55	30	60	NC	NC	NC

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TABLE 5-1. (continued)

Reference	Aerosol	Concen-tration $\mu g/m^3$	MMAD	GSD	N	Subj Char	Exposure Duration	$\dot{V}_E$	Temp°C	RH	SPIR	PLETH	Symptom & Other
Utell et al. (1979)	$NaNO_3$	7000	0.46	1.7	7 11	Normal Asthma	16 min	Rest	Est. 20	25	NC	NC	NC Increased carbachol reactivity
Utell et al. (1980)	$NaNO_3$	7000	0.49	1.7	17	Normal with Influenza	16 min	REST	Est. 20	25	PEF 40% TLC-12% Remained Depressed for one week	SGaw -17%	NC
Utell et al. (1982)	Three sulfates	100	0.5-1.0	1.5-2.2		16 Normal 17 Asthmatic	16 min				NC	NC	NC
	$(NH_4)_2SO_4$ NH_4HSO_4 H_2SO_4	1000 1000 1000	0.5-1.0	1.5-2.2		16 Normal 17 Asthmatic	16 min				NC NC Decreased maximum expiratory flow	NC SGaw-3% SGaw-5%	NC NC Increased carbachol reactivity in normals and asthmatics related to acidity of aerosol
Utell et al. (1983)	$NaHSO_4$	100, 450 1000									NC	NC	NC
	$(NH_4)_2SO_4$	100, 450 1000									NC	NC	NC
	NH_4HSO_4	100, 450 1000	0.8	1.5-2.2	17	Asthmatic NS No Steroid Daily BD	16 min	Rest Mouthpiece	--	25%	NC	SGaw-13%	Increased carbachol reactivity
	H_2SO_4 H_2SO_4	100 450									NC	NC SGaw-19%	NC Increased carbachol reactivity
	H_2SO_4	1000									$FEV_{1.0}$-5% PEF 60% TLC decreased	SGaw-21%	Increased carbachol reactivity

(continued on the following page)

TABLE 5-1. (continued)

Reference	Aerosol	Concentration $\mu g/m^3$	MMAD	GSD	N	Subj Char	Exposure Duration	$\dot{V}_E$	Temp°C	RH	SPIR	PLETH	Symptom & Other
Utell et al. (1984)	H_2SO_4	1000	0.6-1.0	1.5-2.2	14	Normal NS	16 min	Rest Mouthpiece		25%	NC	NC	Increased carbachol activity
	other sulfates as in 1983 (above)		0.6-1.0	1.5-2.2	14	Normal	16 min	Rest		25%	NC	NC	NC
Utell et al. (1985)	H_2SO_4	100 450	0.8	1.7	14	Normal NS	4h, IE 3 x 10 min	EST 25	24	20	NC NC	NC NC	NC Carbachol reactivity increased at 24 H post sore throat reported
Utell et al. (1986)	H_2SO_4	100 450	0.8	1.7	11	Asthmatic	4h, IE (Chamber)	18-35	24	20			Comparable to mouthpiece exposures no details
Utell et al. (1987)	H_2SO_4	100 450	0.8 1.1	1.8 2.0	11	Carbachol sensitive	1h with 10 min ex	EST 30	22	32	NC NC	NC SGaw-14%[a]	NC
		100 450	1.1	2.0	17	Asymptomatic Asthmatics	16 min	REST Mouthpiece	--	25	NC NC	NC SGaw-16%[a]	NC

IE = Intermittent exercise
2X = Two times resting ventilation of ~20 L/min
NC = No Change
SBN2 = Single Breath Nitrogen Washout
RT = Thoracic resistance
H = Hours of Exposure
VMD = Volume median diameter, μm
[a]Corrected for NaCl exposure
PEF = Peak expiratory flow
RF = Respiratory frequency
TV = Tidal volume

MMAD = Mass Median Aerodynamic Diameter, μm
GSD = Geometric Standard Deviation
RH = Relative Humidity %
SPIR = Spirometry
PLETH = Plethysmography
$\dot{V}_E$ = Ventilation during exposure L/min
EX = Exercise
TLC = Total lung capacity
SGaw = Specific airway conductance
$FEV_{1.0}$ = Forced expiratory volume in 1 second
N = Number of subjects

NS = Nonsmoker
BD = Bronchodilator
Est. = Estimated at
M = Male
F = Female
MMEF = Maximum mid-expiratory flow
MMFR = Maximum mid-expiratory flow rate
$\dot{V}_{50}$ = Maximum flow rate calculated at 50% at expired vital capacity

5.4 EXPOSURE TO MIXTURES OF ACID AEROSOLS WITH OTHER POLLUTANT GASES

In the ambient environment, many pollutants coexist. When individuals are exposed to two or more inhaled pollutants, either simultaneously or sequentially, there is potential for an additive or interactive effect. These possible combined effects have been studied for sulfuric acid aerosol in combination with O_3, SO_2, and NO_2. Although a variety of pollutant combinations have been utilized, rarely, if ever, are the ambient conditions approximated. More consideration of actual ambient conditions is required, especially consideration of the gas and aerosol concentrations in areas impacted by plumes.

Kleinman et al. (1981a) studied the effect of the combination of ozone (0.37 ppm), SO_2 (0.37 ppm), and sulfuric acid aerosol (100 $\mu g/m^3$) under warm, humid conditions in an environmental chamber. Nineteen subjects participated in the 2-h intermittent exercise exposures using a non-randomized exposure sequence: exposure to the pollutant was always preceded several days earlier by a clean air "sham" exposure. Exposure to the pollutant mixture caused significant reductions in FVC (-2.8 percent), $FEV_{1.0}$ (-3.7 percent), and other spirometric measurements. There was a trend for symptoms to increase during the exposures but the symptoms reported during the pollutant mixture exposures were not significantly different from those reported during the clean air exposures. The authors indicated that more than 90 percent of the H_2SO_4 was partially neutralized to ammonium bisulfate. The decrease in $FEV_{1.0}$ (-3.7 percent) was only slightly larger than for a previous group of subjects exposed to ozone alone ($FEV_{1.0}$; -2.8 percent), using a similar exposure protocol. It was therefore concluded that the presence of sulfuric acid aerosol did not enhance the effects of ozone-SO_2 mixtures.

Kulle et al. (1982) reported the results of a study in which ozone and sulfuric acid exposure were combined in a sequential manner; the 4-hr exposure to sulfuric acid aerosol was preceded by a 2-h exposure to 0.3 ppm ozone. Twelve nonsmokers participated in this study in which the effects of 0.3 ppm ozone and 100 $\mu g/m^3$ of 0.13 μm sulfuric acid aerosol were studied individually and then in combination. The order of exposures was identical for all subjects: ozone, sulfuric acid aerosol, and ozone plus sulfuric acid aerosol, each exposure separated by one week. The exposures each included one 15 min period of moderate cycling exercise. None of the exposures produced significant changes in spirometry or plethysmography. The authors suggested that the bronchial reactivity to methacholine may have decreased following sulfuric acid aerosol exposure but the apparent difference was not statistically significant. It was concluded that the prior exposure to ozone did not enhance the response to sulfuric acid aerosol (or at least did not help to induce a response where none was previously evident). It was nevertheless suggested that the use of a larger-particle-size sulfuric acid aerosol may have produced different results since a larger aerosol would tend to deposit by impaction to a greater extent on the larger airways, the apparent site of the symptomatic effects of ozone.

In a study involving a total of 231 subjects, Stacy et al. (1983) examined the effects of 4-h exposures to sulfuric acid aerosol (100 $\mu g/m^3$), ammonium sulfate aerosol (133 $\mu g/m^3$), ammonium bisulfate aerosol (116 $\mu g/m^3$), and ammonium nitrate aerosol (80 $\mu g/m^3$) in combination with ozone (0.4 ppm), NO_2 (0.5 ppm) and SO_2 (0.75 ppm). In addition to exposures to each individual pollutant, there were a total of 12 combination exposures to a mixture of one of the four aerosols and one of the three gaseous pollutants. There were two 15-min periods of moderately heavy exercise during the exposure. With the exception of the ozone plus aerosol exposures, none of the aerosols or gas-aerosol mixtures caused any significant changes in plethysmography or spirometry. Similarly, only subjects exposed to ozone reported symptoms indicative of respiratory tract irritation (e.g., coughing or throat irritation).

Kagawa (1986) recently reported the results of a series of studies of exposure to air pollutant combinations, some of which included sulfuric acid aerosol. The subjects were young adult Japanese; approximately half were smokers. A 2-h intermittent exercise protocol was used which included four 15-min exercise periods at 50 W (300 kpm). Exposures to either 200 or 400 $\mu g/m^3$ sulfuric acid aerosol occurred in a body plethysmograph maintained at 28 to 29°C and 50 to 60 percent RH. Unfortunately the data for individual exposures to only sulfuric acid aerosol are omitted from the tables and figures. The addition of sulfuric acid aerosol to exposure atmospheres -- most contained ozone (0.15 to 0.30 ppm) -- produced no obvious additional effects on specific airway conductance over and above those caused by the other pollutants. Airway reactivity to acetylcholine was determined after one series of exposures to 200 $\mu g/m^3$ of sulfuric acid aerosol; no effect on airway reactivity was observed. In several different series of ozone plus sulfuric acid aerosol exposures, the author observed no apparent health-related synergistic effects of sulfuric acid aerosol with ozone.

Horvath and co-workers (1987) studied the effects of exposure to much higher concentrations of sulfuric acid aerosol (1,200 to 1,600 µg/m^3) in combination with ozone. As indicated in Section 5.2, there was no effect of the sulfuric acid aerosol alone on pulmonary function. The combination of a "no-effect level" of ozone with the sulfuric acid aerosol also produced no significant changes in pulmonary function. Although the investigators chose a somewhat conservative probability level for indicating significance ($P < 0.01$), their findings of no significance would also have held at $P < 0.05$.

The studies cited in this section examined the pulmonary function responses to exposure to sulfuric acid aerosol, over a broad range of concentrations, in combination with various other pollutants including ozone, nitrogen dioxide, and sulfur dioxide. There was no evidence to suggest an interactive effect between sulfuric acid aerosol and the other pollutants. However, these studies primarily used the physiological measurement endpoints derived from spirometry or plethysmography. Further studies using different endpoints should be considered.

5.5 EXPOSURE TO OTHER ACID AEROSOLS OR MIXTURES OF AEROSOLS

Human exposure to a number of aerosol species including sodium nitrate ($NaNO_3$), ammonium nitrate (NH_4NO_3), ammonium bisulfate (NH_4HSO_4), ammonium sulfate ($(NH_4)_2SO_4$), zinc ammonium sulfate ($ZnSO_4$-$(NH_4)_2SO_4$), and ferric sulfate ($Fe_2(SO_4)_3$) has been studied over the past several years. Ambient levels of airborne nitrate salts are typically less than 5 µg/m^3 and rarely exceed 50 µg/m^3 (Sackner et al., 1979).

5.5.1 Nitrates

A series of sodium nitrate and ammonium nitrate aerosol exposures in both normals and asthmatics was performed by Sackner and colleagues (1979). Groups of 5 or 6 normal or asthmatic subjects breathed NaCl or $NaNO_3$ aerosol at concentrations ranging from 10 to 1,000 µg/m^3 for 10 minutes while resting. In the normal subjects, possibly significant differences in $\dot{V}_{50\%}$, VC and SGaw between $NaNO_3$ and NaCl exposures were observed. However, a decrease in flow was accompanied by an increase in airway conductance. Because of the large number of specific comparisons, the authors concluded that these observations were probably due to chance alone. They concluded that $NaNO_3$ exposure up to 1,000 µg/m^3 caused no acute effects on cardiopulmonary function.

Utell et al. (1979) studied both normal and asthmatic volunteers exposed to 7,000 μg/m^3 of 0.46 μm $NaNO_3$ aerosol for 16 min via mouthpiece. The major health effect endpoints measured in their study included airway resistance, both full and partial expiratory flow-volume curves, airway reactivity to carbachol, and aerosol deposition. Aerosol deposition as a percentage of inhaled aerosol averaged about 50 percent for normals and about 56 percent for asthmatics; the group differences were not significant. The effect of exposure to $NaNO_3$ aerosol was indistinguishable from the control NaCl exposure in normals. Similarly, there were no effects of $NaNO_3$ exposure in asthmatics.

Utell et al. (1980) subsequently studied 11 subjects with influenza exposed to the same $NaNO_3$ regimen as above. The subjects were initially exposed at the time of illness and then reexposed 1, 3, and 6 weeks later. Aerosol deposition ranged from 45 to 50 percent over the four exposure sessions. All subjects had cough and fever and 10 of 11 had viral or immunologic evidence of acute influenza. Baseline measurements of FVC and $FEV_{1.0}$ were within normal limits and did not change throughout the six-week period. There were small but significant decreases in airway conductance following $NaNO_3$ inhalation. This difference was present during acute illness and one week later but was not seen at 3 and 6 weeks post-illness. The decrease in SGaw seen on the initial exposure was accompanied by a decrease in partial expiratory flow at 40%TLC; this was also observed at the one week follow-up exposure. This study suggests that the presence of an acute viral respiratory tract infection may render humans more susceptible to the acute effects of nitrate aerosols. Nevertheless, the concentration of nitrates used in this exposure study exceeded maximum ambient levels by more than 100-fold.

In addition to $NaNO_3$ aerosols, NH_4NO_3 exposure has been studied by Kleinman and associates (1980). Twenty normal and 19 asthmatic subjects were exposed to a nominal 200 μg/m^3 of 1.1 μm ammonium nitrate aerosol. The 2-h exposures included mild intermittent exercise and were conducted under warm conditions (31°C, 40 percent RH). There were no significant physiologically meaningful effects of the NH_4NO_3 exposure in either subject group.

5.5.2 Other Sulfates

Linn et al. (1981) studied a group of 21 normal and 19 asthmatic subjects exposed to 15 to 16 μg/m^3 of zinc ammonium sulfate aerosol. Exposures lasted 2 h in an environmental chamber at 20°C and 85 percent RH and included light intermittent exercise. Although there were some very small changes in function between and within exposure conditions which apparently reached statistical significance, there was no overall pattern of response which indicated that zinc ammonium sulfate resulted in pulmonary dysfunction. The authors concluded that this study "fails to demonstrate convincingly any effects of zinc ammonium sulfate exposure important to health."

In a subsequent study with zinc ammonium sulfate, Kleinman and co-workers (1985) exposed 20 normal subjects to a mixture of SO_2 (0.5 ppm), NO_2 (0.5 ppm), and zinc ammonium sulfate (26 $\mu g/m^3$, 1.1 μm) combined with NaCl aerosol; these 2-h exposure sequences incorporated light intermittent exercise. There were no significant pulmonary function effects of this exposure. Symptom data suggested that the SO_2-NO_2- (NaCl aerosol-zinc ammonium sulfate) aerosol mixture was somewhat more irritating than the NaCl aerosol alone but the difference was not significant. Only the total symptom score was reported and thus the individual symptoms responsible for the increased score cannot be ascertained from this report. This study confirms the absence of effect of zinc ammonium sulfate observed in the prior Linn et al. (1981) study.

Another metal-sulfate aerosol that has been evaluated as a potential respiratory irritant is ferric sulfate (Kleinman et al., 1981b). Twenty normal and 18 asthmatic subjects were exposed to 75 $\mu g/m^3$ of 2 μm $Fe_2(SO_4)_3$ aerosol. In the presence of ammonia, ferric ammonium sulfate may be formed, which was assumed to be the case in this study. There were no statistically significant changes in the physiologic tests performed before and after the exposures (these included spirometry, plethysmography, single breath nitrogen washout, forced oscillation, and oxygen saturation). Neither normal nor asthmatic groups reported a significant increase in symptoms as a result of the exposure to ferric sulfate. Even when data were analyzed on an individual basis, there was no consistent pattern indicative of dysfunction induced by the ferric sulfate aerosol.

Kulle and co-workers (1984) examined the possibility that a mixture of SO_2 (1.0 ppm) and ammonium sulfate (528 $\mu g/m^3$, 1 μm) could produce greater effects on the respiratory system than either pollutant alone. The exposures lasted 4 h and included two 15-min sessions of moderate bicycle exercise. Twenty subjects (10 M, 10 F) completed the study. There were no significant changes in spirometry, plethysmography, or airway reactivity to methacholine with either ammonium sulfate alone or ammonium sulfate plus SO_2. Nevertheless, there were increased symptoms as a result of the combined exposure in particular, in which 9 of 20 subjects reported upper airway irritation. Only 4 of 20 subjects reported upper respiratory tract symptoms for SO_2 exposures alone. This observation suggests that the upper respiratory symptoms observed in normals after SO_2 exposure (Witek et al., 1985) could possibly be enhanced in the presence of ammonium sulfate.

While testing the hypothesis that a carbon aerosol could potentiate the conversion of SO_2 to sulfates and enhance the effect of SO_2, Kulle and associates (1986) exposed subjects to a mixture of SO_2 (1 ppm) and 500 $\mu g/m^3$ of 1.5 µm activated carbon aerosol. Although it was demonstrated that most of the SO_2 which was sorbed onto the carbon was converted to sulfate, the sorption of SO_2 by carbon constituted only a very small fraction of the total SO_2 dose. The effects of SO_2, which are not of interest for the purposes of the current document, were neither enhanced nor mitigated by the addition of carbon aerosol. This study provided no evidence to support the hypothesis that the inert aerosol worsened the effects of SO_2 in normal healthy subjects as a result of sulfate formation.

These studies of exposure to a variety of sulfate and nitrate aerosols point to the absence of an effect on spirometry, plethysmography, and various other physiological indicators of pulmonary function in asthmatics and healthy normal subjects. The only group of subjects which demonstrated a possible effect were a group of normal individuals who had recently contracted influenza. The health significance of the small alterations in pulmonary function as a result of exposure to "massive" concentrations of $NaNO_3$ is unclear at this time. Even at concentrations much higher than would be anticipated in the ambient air, the nitrates and sulfates that have been studied to date do not appear to produce any meaningful effects on pulmonary function measurements in exposed individuals.

5.6 EFFECTS OF ACID AEROSOLS ON RESPIRATORY FUNCTION OF ASTHMATICS

The effects of sulfuric acid aerosol in asthmatics have been studied in a number of laboratories in the past decade. There is considerable variability in the results of these studies, much of which may be attributed to variability in severity of asthma, in the procedures for withholding or continued use of medication, and in exposure conditions. Asthmatics represent a "sensitive subgroup" who are potentially more susceptible to the effects of several air pollutants. One of the more obvious examples is the approximately tenfold greater sensitivity of asthmatics to SO_2, a gas that not only is a precursor of sulfuric acid aerosol but is also likely to coexist with H_2SO_4. Asthmatics also show increased airway resistance as a result of other stimuli such as exercise, or from breathing cold air, dry air, or hyposmolar aerosols.

The cause of increased resistance is often presumed to be in large conducting airways (bronchoconstriction). However, constriction of the larynx or of smaller airways may make an important contribution to increased airway resistance. The regionalization of changes in airway resistance is not typically evaluated.

Characteristics of the asthmatics who participated in the studies reported in this section are shown in Table 5-2.

Sackner and associates (1978) performed a series of sulfuric acid aerosol exposure studies in a diverse group of 17 asthmatics exposed to 10, 100, and 1,000 $\mu g/m^3$. Most of the asthmatics were taking theophylline, prednisone, or both. The exposures to 0.1 to 0.3 µm sulfuric acid aerosol lasted for 10 min. None of the physiological tests performed showed evidence of significant dysfunction resulting from the exposures.

Avol et al. (1979) exposed 6 asthmatic subjects to 100 $\mu g/m^3$ sulfuric acid aerosol for 2 h on two consecutive days. These subjects were also exposed to ammonium sulfate and ammonium bisulfate. There were no significant group effects on lung function that could be attributed to any of the aerosols. It was noted, however, that two of the asthmatics exposed to sulfuric acid aerosol showed "possibly meaningful changes in respiratory resistance." Because these changes were observed on both sulfuric acid aerosol exposure days, it is unlikely that the responses were due to chance alone. There was a tendency for group mean symptom responses to increase on the sulfuric acid aerosol exposure days. Nevertheless, the authors concluded that there were "no obvious group or individual reactions."

Utell et al. (1982, 1983) studied 17 asthmatics (none requiring steroid therapy) exposed to a variety of aerosols including NaCl, $NaHSO_4$, $(NH_4)_2SO_4$, NH_4HSO_4, and H_2SO_4. The aerosols were submicrometer (0.5 to 1.0 µm) and concentrations were 100, 450, and 1,000 $\mu g/m^3$. The relative humidity was maintained below 25 percent. H_2SO_4 deposition ranged from 54 to 62 percent of the inhaled aerosol. All asthmatics were initially reactive to carbachol inhalation challenge. Following the 16-min exposures to any of the sulfate aerosols none of the asthmatics reported symptoms at any of the concentrations.

TABLE 5-2. SUMMARY OF CHARACTERISTICS OF ASTHMATIC SUBJECTS PARTICIPATING IN ACID AEROSOL STUDIES (1979-1987)

Reference	Age	Number	Mean* or Range		Major Medications	Medication Exclusions	Medication Withholding Period	Allergy History	Airway Reactivity
			Baseline SRaw	Baseline $FEV_{1.0}$/FVC					
Avol et al. (1979)	40.7 35.5 35.5	6 6 6	-- -- --	56* 66* 71*	--	no oral bronchodilators during study	--	--	--
Avol et al. (1986)	20 - 35	9 F, 13 M	2.4 - 22.6	45 - 98	8 IB, 5 OB	--	--	Y	MET
Balmes et al. (1987)	21 - 41	6 F, 6 M	--	61 - 89	3 ST, 12 IB, 40 B	--	24 h	--	Hypoosmolar saline
Fine et al. (1987)	23 - 29	6 F, 2 M	~4 - 25	72*	5 IB, 3 OB	--	12 h	--	MET
Horstman et al. (1986)	18 - 35	6 M	7.2*	66*	--	steroids cromolyn	OB - 24 h IB - 12 h	Y	MET
Koenig et al. (1983)	12 - 17	4 F, 6 M	--	2.99 ± 0.63L*	10 OB, 9 IB 2 CROM, 1 ST	--	4 h	Y	EXER
Koenig et al. (1985)	14 - 18	5 F, 5 M	--	--	7 OB, 7 IB 1 ST	--	4 h	Y	EXER
Koenig et al. (1987)	12 - 18	3 F, 6 M	--	3.41 ± 0.95L	--	--	4 h	Y	MET, EXER
Linn et al. (1986)	18 - 34	9 F, 18 M	4.66*	79*	16 IB, 7 OB 1 ST	--	AH, 48 h OB, 12 h IB, 8 h	Y	COLD, SO_2
Sackner et al. (1978)	~60	7	--	~48*	6 ST, 7 IB, OB	--	8 h	--	--
	~52	8	4.17*	79*	4 ST, 4 IB/OB	--	8 h	--	--
	~58	7	--	--	6 ST 6 IB/OB	--	8 h	--	--
Spektor et al. (1985)	22 - 59	4 F, 6 M	6 - 25	46 - 87	3 OB, 2 IB 1 ST	--	6 h	Y	--
Utell et al. (1979) (1982) (1983) (1984) (1986) (1987)	25 26 27 27 27 27 30	11 17 17 17 12 17 11	5.15* ~5.5* 3.6 - 8.9 5.85* -- 5.32*	78* -- 62 - 79 73* -- --	IB, OB IB, OB IB, OB IB, OB -- --	steroids steroids steroids steroids -- --	24 h 24 h 24 h 24 h -- --	-- -- -- -- -- --	-- CARB CARB CARB CARB CARB

LEGEND:

Age = years
AH = Antihistamine
CARB = carbachol challenge in asthmatic range
EXER = exercise-induced bronchoconstriction
COLD = cold-air-induced bronchoconstriction
$FEV_{1.0}$/FVC = ratio x 100 percent
MET = methacholine challenge in asthmatic range

IB = inhaled bronchodilator, usually a β agonist
OB = oral bronchodilator, usually theophylline
SO_2 = SO_2-induced bronchoconstriction
SRaw = specific airway resistance
ST = steroid, prednisone or beclomethasone
Y = yes, presence of allergy confirmed in most subjects
Number = number of subjects
* = Mean

The low-concentration (100 $\mu g/m^3$) exposure produced no significant group changes. After exposure to the 450 $\mu g/m^3$ dose of sulfuric acid aerosol there was a 19 percent drop in SGaw, compared with only a 3 percent decrease after NaCl aerosol. None of the other pulmonary function parameters was affected by the exposure. Exposure to NH_4HSO_4 aerosol tended to decrease SGaw but the other forms of sulfate aerosol had no significant effect on lung function at the 450 $\mu g/m^3$ level. Following the 1,000 $\mu g/m^3$ exposure series, there was a 21 percent decrease in SGaw with sulfuric acid aerosol and a 13 percent decrease with NH_4HSO_4 aerosol (Figure 5-1). Neither $NaHSO_4$ or $(NH_4)_2SO_4$ produced significant effects. In addition, H_2SO_4 aerosol caused a 5 percent decrease in $FEV_{1.0}$. Both H_2SO_4 and NH_4HSO_4 exposures resulted in significant decreases in flow on both maximum and partial expiratory flow-volume curves.

Ten adolescent asthmatics were exposed via mouthpiece to 110 $\mu g/m^3$ of 0.6 µm sulfuric acid aerosol by Koenig et al. (1983). In contrast to the work of Utell et al. (1983), the studies were carried out under humid conditions (>75 percent RH). The exposure sequence involved 30 min of rest followed by 10 min of moderate exercise (V_E = 40 l/min); NaCl aerosol was used as a control exposure. The regular medication of most subjects included theophylline and a sympathomimetic bronchodilator (2 subjects used cromolyn sodium, 2 used antihistamines, and 1 used prednisone). The hypothesis that there was no difference between the NaCl aerosol and the sulfuric acid aerosol was originally tested by the use of repeated t-tests. This data has been subsequently reanalyzed by the authors (letter on file with ECAO) using an analysis of covariance for repeated measures. There was a tendency for $FEV_{1.0}$, V_{max50}, and V_{max75} to decrease after exposure, both to NaCl aerosol and sulfuric acid aerosol. $FEV_{1.0}$ was decreased 8 percent when measured 2 to 3 min after exercise while breathing sulfuric acid aerosol but was decreased only 3 percent after NaCl aerosol. The analysis of covariance confirmed the significant decreases in $FEV_{1.0}$, $V_{max\ 50}$, and $V_{max\ 75}$ immediately (2-3 min) postexposure. $FEV_{1.0}$ was also significantly reduced 4-5 min after exposure; the flow variables also tended to be reduced after 4-5 min but the changes did not attain statistical significance. The results of the analysis of covariance are presented in Table 5-3.

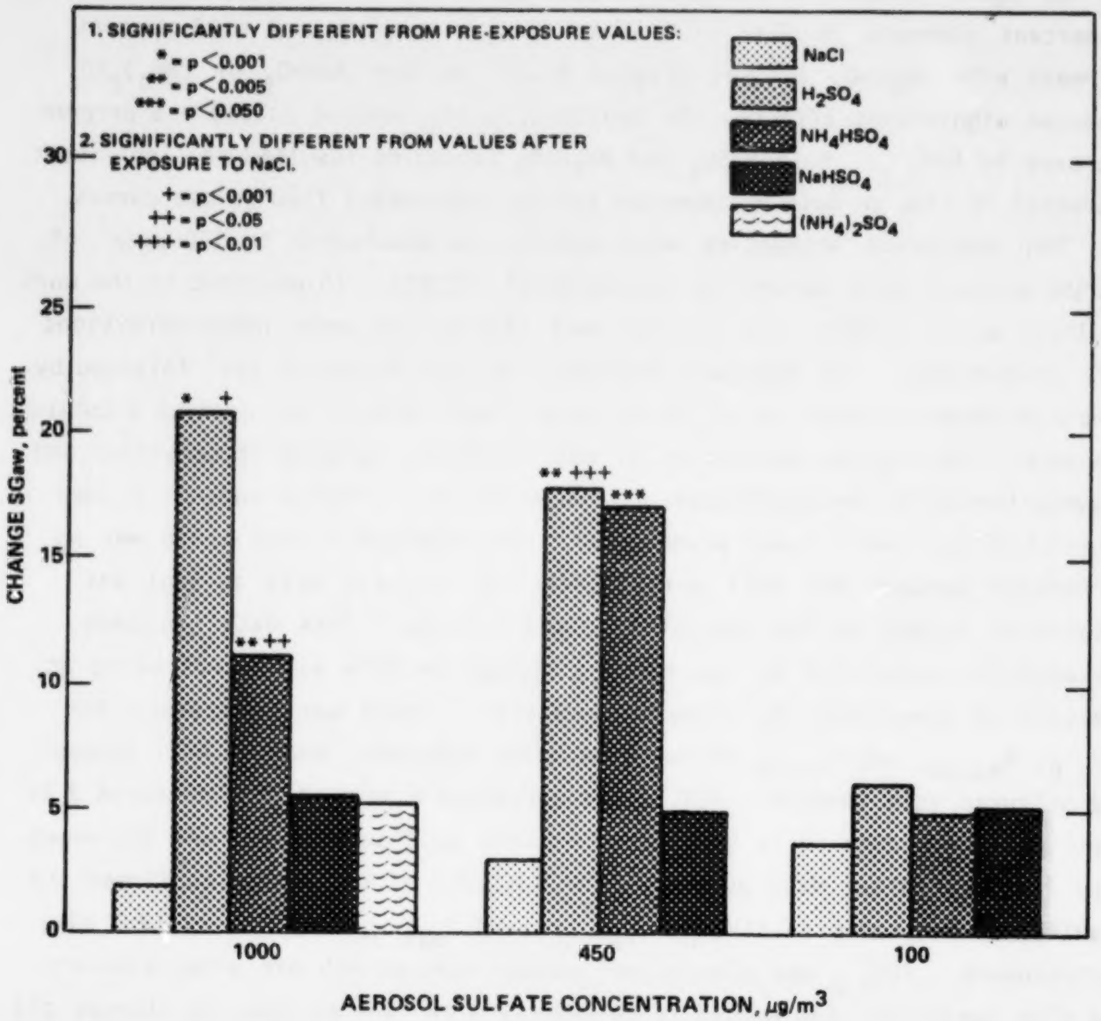

Figure 5-1. Mean percent change in specific airway conductance (SGaw) produced by a 16-minute inhalation of sulfate aerosols by asthmatics.

Source: Utell et al. (1983).

TABLE 5-3. ANALYSIS OF COVARIANCE OF TEN ADOLESCENT ASTHMATICS EXPOSED VIA MOUTH PIECE TO 110 $\mu g/m^3$ SULFURIC ACID AEROSOL

Pulmonary Function Value	Time of Measurement	F	Tail Prob	Adjusted Mean
FEV_1	2-3 min post exp.	20.46	0.0019	H_2SO_4 = 2.68; NaCl = 2.91
	4-5 min post exp.	7.85	0.0231	H_2SO_4 = 2.79; NaCl = 2.92
	later points		N.S.	
$V_{max^{50}}$	2-3 min post exp.	10.23	0.0126	H_2SO_4 = 1.81; NaCl = 2.12
	later points		N.S.	
$V_{max^{75}}$	2-3 min post exp.	6.64	0.0328	H_2SO_4 = 0.66; NaCl = 0.80
	later points		N.S.	
R_T	4-5 min post exp.	3.21	0.1107	H_2SO_4 = 7.32; NaCl = 5.52
	later points also N.S.			

Source: Koenig et al. (1987).

There was also a 40 percent increase from preexposure to postexposure in the forced oscillation measurement of total respiratory resistance (R_T), but the magnitude of this change associated with sulfuric acid aerosol exposure was primarily due to an unusually low preexposure baseline value; the difference in postexposure measurements between NaCl and H_2SO_4 was only 15 percent, which is within the measurement error of this test. The results of this study were compared with a previous study (Koenig et al., 1982) of exposure to 0.5 ppm SO_2 in seven subjects who participated in both studies; the effects of the 0.5 ppm SO_2 exposure were similar to those seen with sulfuric acid aerosol. The investigators concluded that, in this group of adolescent asthmatics, exposure to 100 $\mu g/m^3$ of sulfuric acid aerosol accompanied by exercise led to significant changes in pulmonary function.

In a study aimed primarily at the effects of sulfuric acid aerosol on mucociliary clearance, Spektor and associates (1985) also reported effects on pulmonary function. Ten asthmatics (6 M, 4 F) were exposed to 110, 319, and 971 $\mu g/m^3$ of 0.5 μm sulfuric acid aerosol via nasal mask at 27°C and 47 percent RH. Six mild asthmatics who used no regular medication were designated group I. Four subjects who regularly used methylxanthine and sympathomimetic bronchodilators were designated group II (one of these subjects also used steroids). Following the series of three 20 min inhalations of 1,000 $\mu g/m^3$ of sulfuric acid aerosol in the group I subjects, airway conductance, $FEV_{1.0}/FVC$, $FEF_{25-75\%}$, and V_{max25} were significantly decreased. When measured 3 hours after the exposure, the magnitude of these decreases had become greater; SGaw was decreased 5 percent immediately after exposure and 10 percent after 3 hours. There were no effects of the two lower H_2SO_4 concentrations on respiratory mechanics in these subjects.

In a second study of adolescent asthmatics, Koenig et al. (1985) exposed a different group of 10 subjects to 100 $\mu g/m^3$ sulfuric acid aerosol either via mouthpiece or facemask. Although the intent of the study, in part, was to examine the differences in response to sulfuric acid aerosol between oral and oronasal breathing, this comparison was not made because the subjects reported that they breathed mostly through the mouth (rather than oronasally) when wearing the mask. In addition to other measures of pulmonary function, nasal flow-pressure (power) measurements were obtained. Resting exposures of 30 min were followed by 20 min of moderate treadmill exercise (V_E = 43 l/min). Although associated SO_2 (0.5 ppm) exposures indicated an effect on nasal "power," there was no change in this measurement following sulfuric acid aerosol exposure. $FEV_{1.0}$ was decreased by 7 percent and 8 percent following the two sulfuric acid aerosol exposures but these changes were slightly less than the 9 percent decrease observed with filtered air and considerably less than the 16 to 24 percent decrease after the SO_2 exposure. Although there were significant pre- and postexposure changes in V_{max50} and V_{max75}, there were also large nonsignificant changes in clean air of similar or greater magnitude against which these data were not compared. The use of the repeated t-test in this repeated measures design obscures the effect of changes in respiratory function which occurred with clean air exposures and which are presumably due to modest exercise-induced bronchoconstriction. The results from this study are summarized in Table 5-4.

In more recent work, presented at the 1987 NIEHS Acid Aerosol Symposium, Koenig et al. (1988) indicated that 68 $\mu g/m^3$ sulfuric acid aerosol produced a 5.9 percent decrease in $FEV_{1.0}$. Exposure to a mixture of H_2SO_4 (68 $\mu g/m^3$) and SO_2 (0.1 ppm) produced slightly smaller changes in $FEV_{1.0}$ (-3.5 percent). A small decrease was also observed with clean air exposures; the next decrease with H_2SO_4, after correction for the air exposure, was 4.1 percent. Similarly, $FEF_{50\%}$ was decreased by 13.4 percent (8.2 percent after correction) after sulfuric acid aerosol.

TABLE 5-4. A SUMMARY OF THE PERCENTAGE CHANGE IN PULMONARY FUNCTIONAL VALUES AFTER 10 MINUTES OF MODERATE EXERCISE

Pulmonary Function Value	Exposure Mode Air	Mouthpiece (H_2SO_4)	Mask (H_2SO_4)
R_T	+24 percent NS	+45 percent $p < 0.05$	+35 percent $p < 0.05$
FRC	+8 percent NS	+5 percent NS	+4 percent NS
$\dot{V}_{max50}$	-10 percent NS	-22 percent $p < 0.005$	-16 percent $p < 0.005$
$\dot{V}_{max75}$	-23 percent NS	-18 percent $p < 0.005$	-16 percent $p < 0.010$
FEV_1	-9 percent $p < 0.005$	-7 percent $p < 0.005$	-8 percent $p < 0.005$

NS = nonsignificant.

Source: Koenig et al. (1985).

Linn et al. (1986) studied 27 young adult asthmatics exposed to 0.6 µm sulfuric acid aerosol at three different concentrations (122, 242, and 410 µg/m^3). Studies were conducted in an exposure chamber at 22°C and 50 percent RH; each exposure lasted 60 min and included three 10-min periods of moderate exercise (V_E = 42 L/min). The subjects were a diverse group of asthmatics but all would be considered clinically mild with the exception of one subject who used inhaled steroids. All were sensitive to either cold air inhalation challenge (24 of 27) or 0.75 ppm SO_2 inhalation challenge (23 of 27), and most were sensitive to both challenges. Only 7 of the 27 subjects used regular oral or inhaled medication and all were able to withhold medication prior to exposure (48 h antihistamine, 12 h oral bronchodilators, 8 h inhaled bronchodilators, 8 h steroids). In addition to pre- and postexposure measurements, pulmonary function was also measured after the first 10-min exercise period. In all exposures to sulfuric acid aerosol and clean air there was a significant main effect of time; specifically, pulmonary function tended to worsen with time of exposure regardless of exposure atmosphere. There was no significant effect of sulfuric acid aerosol exposure at any of the concentrations tested. Even when the subjects were divided into reactive and nonreactive groups, there were no apparent differences that could be attributed to acid aerosol exposure. Symptom scores were not significantly affected by the sulfuric acid aerosol exposures, but in the week following the exposure to 410 µg/m^3, the symptom score was "noticeably higher." This observation of an apparently delayed response is in accord with the observations of Utell et al. (1985) and Spektor et al. (1985). The authors concluded that these subjects experienced modest exercise induced bronchoconstriction during these exposures and that these responses were modified only slightly, if at all, by sulfuric acid aerosol inhalation. A preliminary summary of these findings was also reported by Hackney et al. (1986) at the 1985 U.S.-Dutch International Symposium.

Utell et al. (1987) exposed two groups of asthmatics to 100 or 450 µg/m^3 sulfuric acid aerosol either via mouthpiece or while freely breathing in a chamber. There were no effects of exposures to 100 µg/m^3 sulfuric acid aerosol. Resting exposures to 450 µg/m^3 lasted 16 min and resulted in a 19 percent decrease in SGaw. Chamber exposures to 450 µg/m^3 lasted 1 hr and included 10 min of exercise at a power output of 50 watts; SGaw decreased 22 percent after these exposures. The authors estimated that the tracheobronchial deposition of aerosol was 27 µg for mouthpiece and 36 µg for chamber exposures, respectively. Despite the considerable differences in overall respired aerosol mass between the two exposure conditions (72 micrograms -- mouth; 230 micrograms -- chamber), the similarity between the airway responses and the tracheobronchial sulfuric acid aerosol deposition suggested to the authors that a possible causal relationship existed between sulfuric acid aerosol deposition and decreased airway conductance.

Horstman and colleagues (1986) have presented preliminary evidence of a study in which mild asthmatics were exposed to a combination of sulfur dioxide (0.75 ppm) and sulfuric acid aerosol (100 µg/m^3) to determine if small amounts of sulfuric acid aerosol could influence the asthmatic's response to SO_2. The subjects were exposed in a chamber to SO_2 alone, sulfuric acid aerosol alone, and the combination of sulfuric acid aerosol and SO_2, as well as to clean air. Subjects exercised throughout the 20-min exposures at a ventilation of 40 to 44 l/min. under warm (26°C) and humid (70 percent RH) conditions. Because the study was only partially complete when the report was prepared, the investigators did not present statistical analyses of the data. The exercise performed during the exposure produced a modest 75 percent increase in SRaw and a 3.9 percent decrease in $FEV_{1.0}$. The increase in SRaw and the decrease in

$FEV_{1.0}$ were slightly smaller after the H_2SO_4 exposure than after air. After SO_2 exposure, SRaw increased from 7.5 to 29.0 $cmH_2O \cdot s$. After H_2SO_4 plus SO_2 exposure, SRaw increased from 7.1 to 33.1 $cmH_2O \cdot s$. Changes in $FEV_{1.0}$ were also larger after SO_2 or SO_2 plus H_2SO_4, averaging 0.50 and 0.55 liters respectively. It is not clear whether the slightly larger responses after the combined exposure will prove to be significant when the data from the completed study are analyzed. Symptom responses followed a similar pattern to the spirometry and plethysmography measurements in that they were most pronounced with the two exposures involving SO_2. The authors suggested the possibility that the sulfuric acid aerosol could enhance the responses of asthmatics to sulfur dioxide.

Avol et al. (1986) have studied the effects of "acid fog" in both normal and asthmatic subjects. They exposed subjects to nominal concentrations of 0, 500, 1,000 or 2,000 $\mu g/m^3$ of sulfuric acid "fog" aerosol (10 μm) under "fog" conditions (10°C and 100 percent RH). Three 10 minute periods of exercise ($V_E \cong 43$ L/min) were performed during the one hour chamber exposure. Half the subjects gargled grapefruit juice prior to exposure in order to minimize oral ammonia levels. The efficacy of this procedure in reducing oral ammonia was not reported. All asthmatics were clinically mild; less than half used regular medication. The only significant effect of the acid fog exposure appeared to be a decrease in peak expiratory flow after exposure to 2,000 $\mu g/m^3$. There was a trend for $FEV_{1.0}$ and FVC to decrease after the 2,000 $\mu g/m^3$ exposure but these trends were not significant. There were no significant effects attributable to gargling acid juice prior to exposure. Symptoms classified as "lower respiratory" were significantly increased during acid fog exposures, especially at 2,000 $\mu g/m^3$. These symptoms were largely resolved at one hour post exposure. "Upper respiratory symptoms" also increased during the 2,000 $\mu g/m^3$ exposure. Airway reactivity to methacholine was not changed following exposure to any of the concentrations of acid fog. The responses of the asthmatics were similar to those of normals. In this study, it was demonstrated that with larger aerosols, which deposit in the major pulmonary and extra-thoracic respiratory airways, asthmatics were not more reactive than healthy normal subjects.

Hackney et al. (1988) recently presented additional studies of adult asthmatics exposed to nominal concentrations of 500, 1,000, and 2,000 $\mu g/m^3$ of 0.9 μm sulfuric acid aerosol. (Actual high concentration was closer to

1,500 $\mu g/m^3$). Whereas the acid fog studies (Avol et al., 1986) showed increased respiratory symptoms in the absence of changes in spirometry, subjects exposed to the smaller aerosol experienced significant changes in FEV_1 and increased lower respiratory symptoms. These observations are in accord with aerosol deposition models which would predict substantially greater intrathoracic deposition of the smaller aerosol.

Utell et al. (1986) recently summarized the importance of three factors that affect the responses of asthmatics to sulfuric acid aerosols. One of these factors, exercise, is known to exacerbate the effects of most inhaled pollutants due to the increase in ventilation and is also known to produce bronchoconstriction in asthmatics. The mode of breathing (i.e., nasal, oronasal, or mouthpiece) affects the tracheobronchial deposition of inhaled aerosols; the extent to which deposition patterns are altered depends in part upon the initial particle size, the hygroscopic growth of the particle, and the velocity of airflow. Within the size range of ambient sulfuric acid aerosol (0.2-0.6 μm), the deposition is only slightly higher with nasal than with oral breathing. Deposition of aerosol has been demonstrated to be directly related to the observed responses. A third factor that appears to be specifically related to acidic aerosols is the observation that oral and/or respiratory ammonia may mitigate the response to inhaled acid aerosol, because of neutralization of the acid.

These studies on acid aerosol exposure of asthmatics indicate that asthmatics are more reactive than normals to inhalation of these aerosols. The observation was made in several studies (Avol et al., 1979; Utell et al., 1985) that symptoms tended to increase immediately and also with some time delay after sulfuric acid aerosol exposure. It appears that these delayed symptom responses may be more likely to occur after longer exposures, when they may possibly overwhelm the capacity of the respiratory surface liquids to buffer the hydrogen and sulfate ions present in the aerosols. The most acidic sulfate aerosols (i.e., H_2SO_4 and NH_4HSO_4) tended to be the ones that caused the greatest pulmonary function effects. Pulmonary function responses in adult asthmatics have been observed after exposure to 400 to 1,000 $\mu g/m^3$ sulfuric acid aerosol; no pulmonary function effects have been reported for normals below 900 $\mu g/m^3$. Responses for adolescent asthmatics exposed to 68 $\mu g/m^3$ have been reported but these results have not been confirmed in studies of adult asthmatics. Folinsbee (1988) summarized the effects of various concentrations of sulfuric acid aerosol on changes in $FEV_{1.0}$ in asthmatics (Figure 5-2). Studies of asthmatics exposed to "acid fog", even at high sulfuric acid aerosol concentrations do not so far indicate that asthmatics are more reactive than normal subjects to these larger aerosols.

5.7 EFFECT OF ACID AEROSOL INHALATION ON PULMONARY CLEARANCE MECHANISMS

Inhalation of acid aerosols has been shown to alter the pulmonary defense mechanisms, in particular mucociliary clearance and alveolar macrophage function. Animal studies have indicated that the relative potency of sulfates in altering mucociliary clearance $[H_2SO_4 > NH_4HSO_4 > (NH_4)_2SO_4 > Na_2SO_4]$ is related to their acidity (Schlesinger, 1985).

Acid aerosols could alter mucociliary clearance by altering the physical properties of the mucociliary blanket, influencing mucus production, or by altering the beat frequency of the cilia. Physical damage to the cells that produce mucus or damage to the cilia that move the mucous layer would also alter clearance. A reduction in pH of the surface liquid of the trachea and bronchi results in an increase in mucus viscosity and a decrease in the beating frequency of cilia (Schlesinger, 1985) (see Section 4.5.1 and 3.4.1).

Sulfuric acid can either stimulate or inhibit mucociliary clearance, depending on the regional airway dose. Low doses stimulate (slightly more viscous mucus moves more rapidly) and higher doses inhibit (because of decreased ciliary motility) clearance. The effects may vary from place to place within the respiratory system depending on the site of aerosol deposition associated with a given particle (Lippman, 1985). This latter point is of considerable importance in interpretation of the results. For best indication of effects, test aerosols used to measure clearance should deposit in the same region of the lung as the pollutant aerosol. Clearance is typically measured by following the clearance of radioactively labelled particles that have been deposited in the lung by inhalation. External detectors are used to measure the amount of remaining test aerosol at various times following inhalation (see Clark and Pavia, 1980 for discussion of methodology).

In 1978, Newhouse et al. (1978) examined the effects of threshold limit value (TLV) levels of SO_2 (5 ppm) and H_2SO_4 (1,00 $\mu g/m^3$, 0.5 μm) on mucociliary clearance of healthy adults. They measured clearance using a 3 μm aerosol of

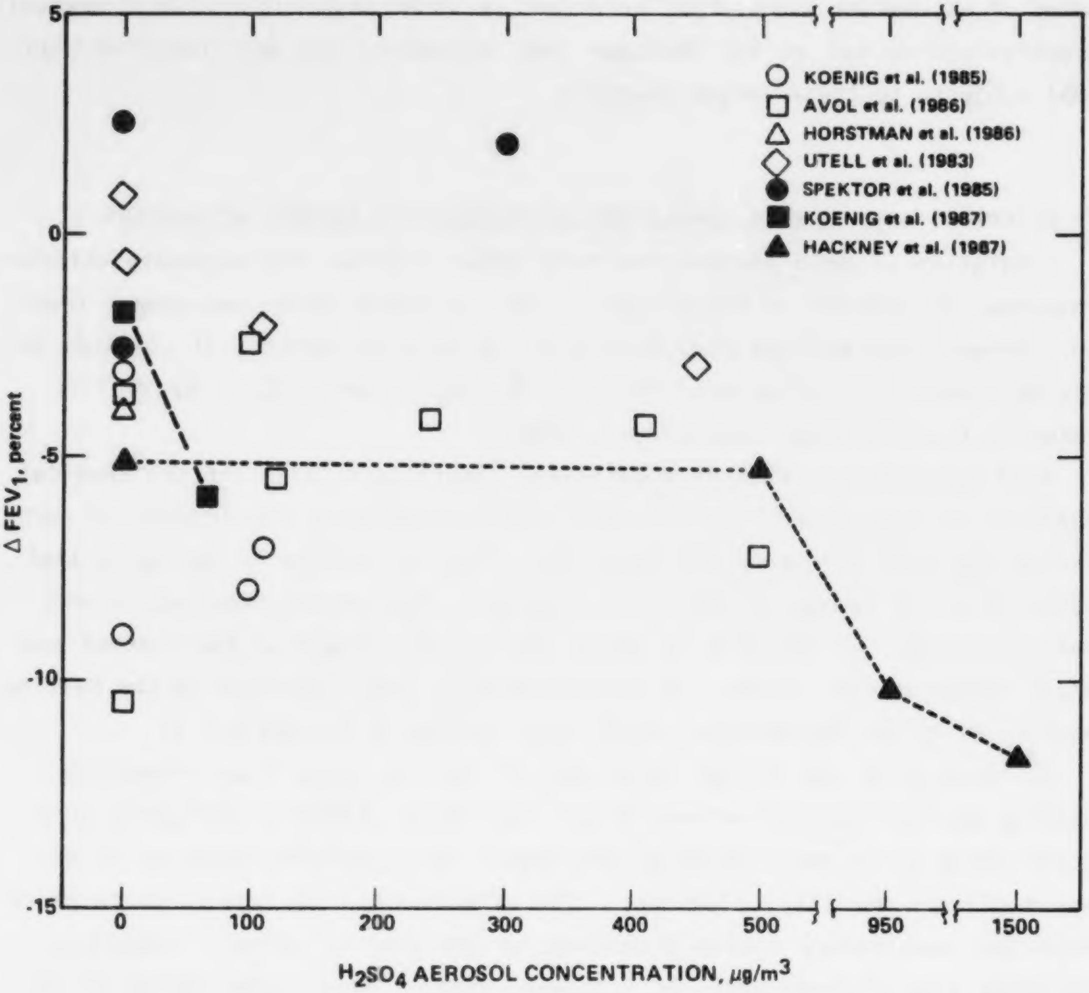

Figure 5-2. Change in FEV_1 in asthmatics exposed to various concentrations and particle sizes of sulfuric acid aerosol. Dashed and dotted lines indicate data for the two studies presented at this symposium. Horizontal axis scale is non-linear.

^{99m}Tc-Albumin in saline administered by a bolus technique intended to achieve deposition in the large airways. The subjects were exposed to either sulfuric acid aerosol or distilled water aerosol in a chamber. Mouth breathing was obligatory throughout. The exposure lasted 2.5 h and consisted of 30 min rest, 30 min intermittent heavy exercise (4 X 5 min at 70 to 75 percent of maximum aerobic power, estimated ventilation 60 to 90 L/min), and 90 min rest. Bronchial clearance was 15 percent faster following the H_2SO_4 exposure than following water aerosol exposure. With the small aerosol used in this study, it is likely that the central airway deposition was minimal. Furthermore, oral breathing would promote neutralization of the sulfuric acid aerosol by ammonia. The combination of a small aerosol MMAD and high levels of oral ammonia would result in a minimization of hydrogen ion deposition in the central airway. Since the test aerosol was intended to measure central airway clearance, the measurements were made at a site different from that where the sulfuric acid aerosol was deposited. It is known that small amounts of sulfuric acid aerosol can stimulate central airway clearance but the effects of sulfuric acid aerosol on peripheral airway clearance in the subjects of Newhouse et al. (1978) is unknown.

Leikauf et al. (1981) studied the responses of 10 healthy nonsmokers to distilled water aerosol (sham) or 110, 330, or 980 $\mu g/m^3$ of 0.5 μ sulfuric acid aerosol administered via nasal mask (see Figure 5-3). Following these 1-hr resting exposures, clearance of Fe_2O_3 radioactively labelled with ^{99m}Tc (which was administered prior to exposure) was followed for 7 to 10 hours and then measured again at 24 hours. In addition to measurements of bronchial clearance from the right lung by whole lung imaging, tracheal mucociliary transport rates were also determined by focusing on the head and neck region. There was no effect of sulfuric acid aerosol exposure on tracheal mucociliary transport rates. At the lowest exposure concentration (110 $\mu g/m^3$), the bronchial mucociliary clearance rate (BMCR) was accelerated (clearance half-time was reduced 38 percent). At the highest exposure concentration (980 $\mu g/m^3$), BMCR was apparently significantly slower (clearance half-time increased 48 percent). However, there was a marked variability in the response and the data were analyzed by the use of a paired t-test, which is not appropriate in the case of a repeated measures design such as used in this study. The evaluation of the significance of the paired t-test was not adjusted for multiple comparisons (e.g., Bonferroni), and furthermore the t distribution for one-tailed tests was used. If the more appropriate two-tailed distribution is used, only the change (i.e., increased clearance) at 110 $\mu g/m^3$ is significant using a t-test. A follow-up test on the four subjects with the most rapid baseline clearance was performed. Because much of the clearance in these subjects would have been completed before the sulfuric acid aerosol exposure ended, the tagged Fe_2O_3 was administered after rather than before the 1,020 $\mu g/m^3$ sulfuric acid aerosol exposure. Three of these four subjects had previously demonstrated an apparent acceleration, rather than a depression, of clearance after the 980 $\mu g/m^3$ exposure. After the 1,020 $\mu g/m^3$ exposure, evidence of slowing of mucociliary clearance was seen in three of these four subjects. This study suggested that sulfuric acid aerosol at TLV levels (approximately 1,000 $\mu g/m^3$) causes a depression of mucociliary clearance in healthy nonsmokers. However, the results of this study cannot be considered conclusive because of the flaw in the data analysis methodology and the unfortunate flaw in the experimental design that probably caused the investigators to miss the effects of 980 $\mu g/m^3$ sulfuric acid aerosol exposure in subjects with normally rapid clearance. The effect of sulfuric acid aerosol on clearance was clearly an acute response since there were no differences in 24-h retention of the marker aerosol regardless of the sulfuric acid aerosol exposure concentrations.

An earlier report of the above study was presented by Lippman et al. (1980) at the Fourth Inhaled Particles Symposium. The above study and a series of animal studies with both cigarette smoke and sulfuric acid aerosol exposures were summarized by Lippmann et al. (1982) at the Fifth Inhaled Particles Symposium.

The test aerosol (^{99m}Tc labeled Fe_2O_3) used to measure mucociliary clearance in the initial Leikauf et al. (1981) study had a MMAD of 7.6 µm and deposited primarily in the large bronchi and trachea. However, the 0.5 µm sulfuric acid aerosol deposited primarily in the more peripheral airways. In order to determine the effect on peripheral airway clearance, Leikauf et al. (1984) performed a second study using a smaller test aerosol (MMAD = 4.2 µm) (see Figure 5-3). Five never smokers and three light ex-smokers participated in this study; one ex-smoker had previously contracted pneumonia and one never-smoker had experienced two previous episodes of bronchitis. One-hour exposures via nasal mask were performed in three 20-min segments with brief (3 min) measurement periods interposed between exposure segments. The sulfuric acid aerosol concentrations studied were 0, 110, 310, and 980 $\mu g/m^3$ of 0.5 µm

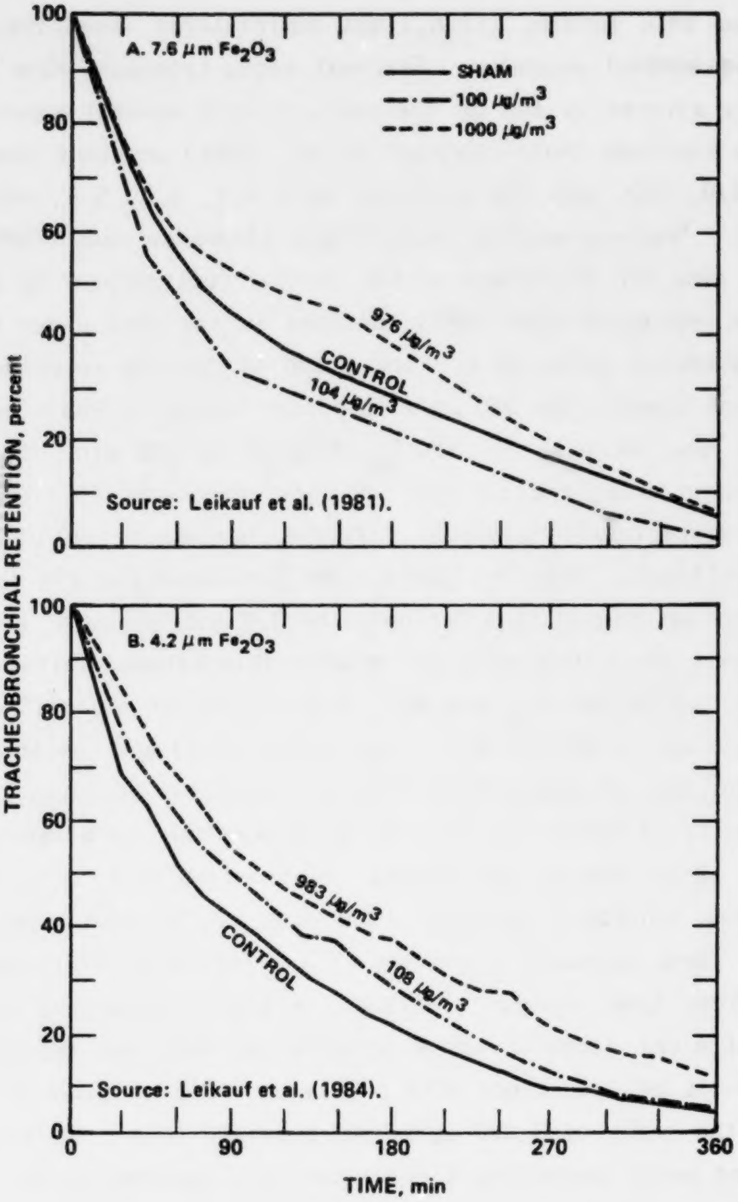

Figure 5-3. Effect of H_2SO_4 aerosol exposure on group mean tracheobronchial mucociliary retention of ^{99m}Tc-labeled Fe_2O_3 particles. A: The response of ten healthy subjects who inhaled a 7.6 μm Fe_2O_3 aerosol before a 1-hr H_2SO_4 aerosol exposure and B: The response of eight healthy subjects who inhaled a 4.2 μm Fe_2O_3 aerosol before a 1-hr H_2SO_4 aerosol exposure.

aerosol. The test aerosol (Fe_2O_3) was administered immediately before the sulfuric acid aerosol exposure. Tracheal mucus transport rate (TMTR) was not significantly altered by any of the sulfuric acid aerosol exposure concentrations, which confirms their (Leikauf et al., 1981) previous observation; TMTR for the 0, 110, 330, and 980 exposures were 5.7, 5.9, 5.0, and 5.5 mm/min, respectively. Tracheobronchial mucociliary clearance rate (TBMC) was assessed by T_{50}, the time for 50 percent of the initial test aerosol to clear the lung, and the mean residence time (MRT), defined as the area under the tracheobronchial retention curve (i.e., the graph of percent retention of marker aerosol versus time). The 980 $\mu g/m^3$ exposure caused marked slowing of TBMC as indicated by the increase in the T_{50} from 80 to 142 min. Clearance was similarly slowed after the 110 and 330 $\mu g/m^3$ exposures (T_{50} increased to 110 and 106 min respectively) although only the increase at 110 $\mu g/m^3$ was statistically significant. Mean residence time increased for all three exposure conditions but was significant for only the 330 and 980 $\mu g/m^3$ exposures. There was no evidence for a dose-response relationship between sulfuric acid aerosol concentration and either T_{50} and MRT, the indices of mucociliary clearance. However, there was a small subject population (n=8) and the inter- and intrasubject variability of mucociliary clearance measures is quite large.

The results of these two studies by Leikauf and co-workers (1981, 1984) suggest that while none of the tested levels of sulfuric acid aerosol affect tracheal mucus transport velocity, low doses (<200 $\mu g/m^3$) may stimulate clearance in large conducting airways (i.e., less than ninth generation) but may at the same time depress clearance in small conducting airways; the regional anatomical location where stimulation ends and depression begins obviously cannot be determined with precision. Higher doses of sulfuric acid aerosol, on the order of 1,000 $\mu g/m^3$ and possibly lower, inhibit clearance in both large and small conducting airways but not, apparently, in the trachea.

To determine whether subjects with hyperreactive airways would demonstrate similar effects on mucociliary transport following sulfuric acid aerosol exposure, Spektor et al. (1985) studied a group of 10 asthmatics exposed to sulfuric acid aerosol levels which were similar to those used for the normal subjects of Leikauf et al. (1981, 1984). Four of the subjects (designated group II) required daily medication (either aminophylline or isoproterenol); one took corticosteroids. All subjects withheld medication for six hours prior to the study except for the steroid-dependent subject. $FEV_{1.0}/FVC$ ranged from

46 percent to 87 percent. The asthmatics not requiring daily medication were designated group I; two of these subjects were current smokers. The exposure techniques were similar to those used by Leikauf et al. (1981, 1984). Resting nasal mask exposures to 0.5 μm sulfuric acid aerosol concentrations of 0, 110, 319, and 971 μg/m^3 lasted for a total of one hour (three 20-min inhalation periods separated by 3-min measurement periods). Tracheal mucus transport rates were within the same range as those reported by Leikauf et al. (1981, 1984) for healthy nonsmokers. There was no significant effect of sulfuric acid aerosol at any of the tested levels on TMTR. For the six subjects who did not require daily medication, TBMC was reduced after exposure to the highest concentration (917 μg/m^3) of sulfuric acid aerosol. Mean retention time of the test aerosol was unaffected by sulfuric acid aerosol, indicating a transient or short-lasting depression of clearance rate. For the subjects requiring daily medication there was no clear pattern of response, although clearance tended to be accelerated rather than depressed.

The authors concluded that the mucociliary clearance of the Group I subjects (mild asthmatics not dependent on medication) was slowed in a dose-dependent manner as a result of the sulfuric acid aerosol exposure. This conclusion was based on the regression of the group mean values for clearance at each of the four concentrations. However, examination of the individual data indicated that an individual dose-response relationship was apparent for only one of the six subjects (who also happened to be a smoker). Mucociliary clearance (T_{50}; time to clear half the aerosol) tended to be slower in the asthmatics than in previously tested normals although mean retention times and TMTR were similar for normals and asthmatics. These results suggest a possible increased risk for asthmatics from the transient reductions of mucociliary clearance since their normal baseline mucociliary clearance tends to be somewhat compromised. The added reduction of clearance as a result of sulfuric acid aerosol exposure resulted in a clearance rate that was less than 50 percent of the baseline clearance rate of normal healthy nonsmokers. However, since two of the six subjects in Group I were current smokers, this comparison may not be valid because of the possible direct or interactive effects of smoking on clearance.

Spektor et al. (1988) have recently completed a study which addresses many of the problems in earlier studies of the effects of acid aerosol on mucociliary clearance (1987 NIEHS Acid Aerosol Symposium). Ten healthy normal subjects were exposed to 100-110 $\mu g/m^3$ of 0.5 μm H_2SO_4 aerosol for 1 hour and 2 hours on separate occasions. A control exposure to distilled water aerosol was also conducted. The gamma-labelled tracer aerosols, used to measure clearance, were varied in size for each subject (range 4.0 to 5.8 μm MMAD) in order to achieve a similar initial deposition pattern of approximately 30 percent alveolar and 70 percent tracheobronchial. A controlled respiratory pattern was used to ensure reproducible deposition of tracer aerosol. Two tracer aerosols were administered to each subject, one tagged with ^{198}Au and the other with ^{99m}Tc. The gold-198 tagged aerosol was administered before exposure to H_2SO_4 and the technetium-99m was administered following acid exposure. Clearance was measured during and for 5 hours after exposure.

There was no difference in tracer aerosol deposition, whether inhaled prior to or after the acid aerosol exposure. This is an important observation for future studies since it demonstrates that the tracer may be administered following exposure when there are no significant alterations in respiratory mechanics, as observed in this study. Furthermore, the clearance measurements indicated a greater effect on clearance when the tagged aerosol was administered after acid exposure. After a 1 hour acid aerosol exposure, average clearance half times increased 100 percent. After a two hour exposure, half time was elevated 162 percent relative to the control. The authors suggested that there was an approximate 40 min delay, after the beginning of acid aerosol inhalation, before there were noticeable alterations in clearance. There was a considerable difference in the persistence of the alterations in clearance, depending on exposure duration. With a 1 hour exposures, clearance was approaching normal rates by 2-3 hours after exposure. However, with the 2 hour exposure, the clearance rate continued to slow for at least 3 hours after the completion of acid aerosol inhalation. These studies clarify and extend previous observations of slowing of mucociliary clearance after acid aerosol exposure. They indicate that the response depends not only on acid concentration but also on duration of exposure.

As part of the summary of human acid aerosol exposure studies presented at the 1987 NIEHS Acid Aerosol Symposium, Folinsbee (1988) presented a figure summarizing changes in clearance half-time as a result of exposure to varying concentrations of sulfuric acid aerosol (Figure 5-4).

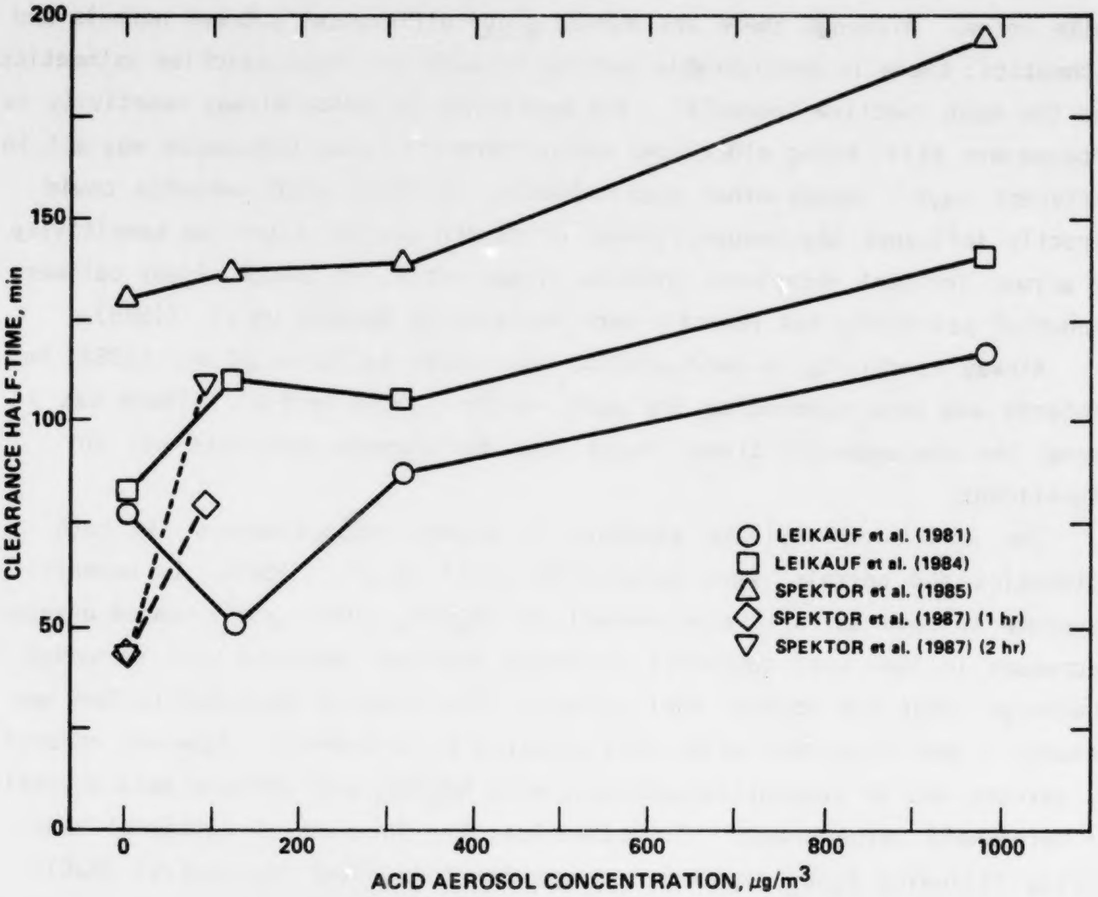

Figure 5-4. Clearance half-time (i. e. time required to clear half the deposited tracer aerosol) as a function of the concentration of acid aerosol to which the subjects were exposed. All exposures were for one hour to 0.5 μm sulfuric acid aerosol, except for the one 2-hour exposure reported by Spektor et al, 1987. Note the broad range of baseline clearance rates.

5.8 EFFECTS OF SULFURIC ACID AEROSOL ON AIRWAY REACTIVITY

Many inhaled substances, including air pollutants, can alter the response of the airways to pharmacologic (e.g., histamine, methacholine, carbachol) or physical (e.g., cold and/or dry air) stimuli that induce bronchoconstriction. The normal range of reactivity to agents that provoke bronchoconstriction is quite large. Although there are marked group differences between normals and asthmatics, there is considerable overlap between the least reactive asthmatics and the most reactive "normals". The mechanisms by which airway reactivity is altered are still being elucidated and different inhaled substances may act in different ways. Among other possibilities, sulfuric acid aerosols could directly influence the responsiveness of smooth muscle, alter the sensitivity of airway irritant receptors, produce airway edema, or change airway caliber. Bronchial reactivity has recently been reviewed by Boushey et al. (1980).

Airway reactivity to methacholine was tested by Kulle et al. (1982) in subjects who were exposed to 100 $\mu g/m^3$ sulfuric acid aerosol. There was a trend for postexposure airway reactivity to decrease but this was not significant.

The effects of sulfate exposure on airway responsiveness, in both asthmatics and normals, were assessed by Utell et al. (1982). In normals, exposure to both sulfuric acid aerosol and NH_4HSO_4 (1000 $\mu g/m^3$) caused greater decreases in SGaw with carbachol challenge than was observed with carbachol challenge after the control NaCl aerosol. The range of decrease in SGaw was between 6 and 13 percent after NaCl exposure (+ carbachol). SGaw was reduced 17 percent and 22 percent respectively with NH_4HSO_4 and sulfuric acid aerosol (+ carbachol) respectively. In asthmatics, the increase in carbachol reactivity following H_2SO_4 exposure was greater than after the control (NaCl) exposure. In addition, Utell et al. (1983) reported that the decrease in SGaw after control carbachol exposures (i.e., an index of baseline airway reactivity) was well correlated with the decrease in SGaw after sulfuric acid aerosol exposures ($r = 0.90$), suggesting that carbachol reactivity may be a good predictor of the bronchoconstrictor response to sulfuric acid aerosol. However, this relationship needs to be examined in a larger subject population with a broad range of response to both carbachol (or another cholinergic agonist) and sulfuric acid aerosol. It was also noted that the most acidic (i.e., H_2SO_4 and NH_4HSO_4) sulfates produced the greatest response.

In normals exposed for 16 min to 100 to 1,000 μg/m^3 of sulfuric acid aerosol (as well as other sulfates), Utell et al. (1984) examined the airway reactivity to carbachol following exposure. Airway reactivity was assessed by comparing airway resistance and spirometry both before and after a five-breath dose of a 1 percent carbachol aerosol. As in the study of Kulle et al. (1982), no effects on airway reactivity were observed after exposure to 100 μg/m^3 sulfuric acid aerosol. However, airway reactivity was increased after exposure to 1,000 μg/m^3 of either sulfuric acid aerosol or ammonium bisulfate aerosol. Using similar exposure conditions, asthmatics were exposed to 100, 450, and 1,000 μg/m^3 sulfate aerosols. Airway reactivity to carbachol was increased in the asthmatics after both 1,000 and 450 μg/m^3 sulfuric acid aerosol exposures. The other sulfates did not alter airway reactivity.

In a subsequent study (Utell et al., 1985), the effects of 100 and 450 μg/m^3 sulfuric acid aerosol on airway reactivity was reexamined. In this study, normal subjects participated in 4-hour exposures that incorporated three 10-min periods of mild exercise. Airway reactivity to carbachol was measured immediately after exposure and again at 24 hours postexposure. Immediately after exposure, airway reactivity was unchanged. However, 24 h after the 450-μg/m^3 exposure, carbachol reactivity was increased; the response to the carbachol challenge was a -21 percent reduction in SGaw. Twenty-four hours after NaCl aerosol exposure, the same carbachol challenge caused only a -8 percent reduction in SGaw. In addition, at the 24-h test, 8 of the 14 subjects reported throat irritation that had first been noticed between 12 and 24 hr postexposure. As in the previous study, there were no immediate or delayed effects of exposure to 100 μg/m^3 sulfuric acid aerosol. The results of the above studies were more recently summarized by Utell and Morrow (1986).

The airway reactivity to a cold air challenge following sulfuric acid aerosol exposure in asthmatics was recently reported by Linn et al. (1986). One-hour exposures to 0, 122, 242, and 410 μg/m^3 sulfuric acid aerosol were followed by a cold air challenge. The subjects breathed subfreezing air for 4 min, and the response was determined by the percent decrease in $FEV_{1.0}$. There was no difference in response among the four exposure conditions; sulfuric acid aerosol did not exacerbate the bronchoconstriction caused by breathing cold-dry air.

These reports of altered airway reactivity in both normals and asthmatics exposed to sulfuric acid aerosol may indicate altered responsiveness of one or more components of the bronchoconstriction reflex arc, such as airway receptors or airway smooth muscle. The effects occurred at concentration levels similar to those at which changes in airway conductance or spirometry have also been demonstrated. Change in airway reactivity may be an indirect indicator of inflammation in the airways or of disruption of the normal status of the airway epithelium.

5.9 SUMMARY AND CONCLUSIONS

Normal subjects have been exposed to sulfuric acid aerosols ranging in concentration from 10 to approximately 1,500 $\mu g/m^3$ under both resting and intermittent exercise conditions. No effects of spirometry or plethysmography have been observed after exposure to concentrations of less than 500 $\mu g/m^3$. Small changes in spirometry have been observed after exposures to approximately 1,000 $\mu g/m^3$ but these changes have not been consistently observed. Responses to extended exposures (e.g., 6 to 8 hours) at lower concentrations should be evaluated.

Exposure studies in man have been conducted using a number of different sulfate and nitrate aerosols. Studies of exposure to a variety of sulfate and nitrate aerosols point to the absence of an effect on spirometry, plethysmography, and various other physiological indicators of pulmonary function in asthmatics and healthy normal subjects. Exposures to combinations of sulfates with other pollutant gases, most notably ozone and SO_2, have not demonstrated any evidence of synergistic or interactive effects with endpoints that have been measured in human exposure studies.

Asthmatics have been exposed to a range of sulfuric acid aerosol concentrations from 10 to 1,000 $\mu g/m^3$. Exposures to concentrations of approximately 400 to 1,000 $\mu g/m^3$ typically produced modest bronchoconstriction and small decrements in spirometry. At aerosol concentrations near 100 $\mu g/m^3$, small decrements in spirometry have been observed for adolescent, but not for adult, asthmatics. More information is required for asthmatics exposed to sulfuric acid aerosol at lower concentrations ($<200\ \mu g/m^3$) for extended periods (4 to 8 hours).

There is a suggestion in studies of normals and asthmatics that there may be delayed responses to sulfuric acid aerosol in addition to the acute responses measured immediately after exposure. These delayed responses may include both symptomatic and functional effects that persist or worsen within the 24-hour period following exposure. The delayed responses appear more likely to follow longer duration exposures (i.e., 1 to 4 hours with exercise) rather than brief resting exposures. These observations suggest that, while small quantities of acid aerosol may be neutralized by ammonia or buffered by airway surface liquids, larger quantities of acid aerosol may cause more persistent changes in airway surface pH and hence may be more toxic. Further study of the possible mechanisms and potential importance of delayed effects is needed.

The effects of sulfate and nitrate aerosols appear to be related to their acidity or more specifically their titratable acidity. High levels of oral or respiratory ammonia tend to reduce the effects of inhaled acidic aerosols. Furthermore, unbuffered aerosols have less effect than buffered aerosols of the same pH, suggesting that alteration of airway surface pH may be one of the stimuli provoking cough and bronchoconstriction.

Inhalation of high concentrations (1,000 $\mu g/m^3$) of sulfuric acid aerosol cause a reduced rate of mucociliary clearance in both normals and asthmatics. This is an acute response and does not affect the overall retention of aerosol (over a 24-hour period). The acid aerosol has no apparent effect on tracheal mucociliary transport rates measured in the most proximal portion of the main airway. Additionally, low doses of sulfuric acid aerosol may result, initially, in an increased rate of mucociliary clearance in the major airways of both normals and asthmatics. Effects on H_2SO_4 on slowing of mucociliary clearance in small airways begin at concentrations as low as 100 $\mu g/m^3$.

Airway reactivity to bronchoconstrictive drugs such as carbachol or methacholine is increased after exposure to 1,000 $\mu g/m^3$ of sulfuric acid aerosol in both normal and asthmatic subjects. 100 $\mu g/m^3$ of H_2SO_4 does not appear to alter airway reactivity in either normals or asthmatics. Intermediate concentrations (~500 $\mu g/m^3$) may result in either immediate or delayed (post -24 h) increases in airway reactivity.

5.10 REFERENCES

Amdur, M. O.; Melvin, W. W.; Drinker, P. (1953) Effects of inhalation of sulphur dioxide by man. Lancet 2: 758-759.

Avol, E. L.; Jones, M. P.; Bailey, R. M.; Chang, N.-M. N.; Kleinman, M. T.; Linn, W. S.; Bell, K. A.; Hackney, J. D. (1979) Controlled exposures of human volunteers to sulfate aerosols: health effects and aerosol characterization. Am. Rev. Respir. Dis. 120: 319-327.

Avol, E. L.; Linn, W. S.; Hackney, J. D. (1986) Acute respiratory effects of ambient acid fog episodes: final report. NIEHS grant no. ES03291-02; September.

Balmes, J. R.; Fine, J. M.; Gordon, T.; Sheppard, D. (1988) Potential bronchoconstrictor stimuli in acid fog. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Boushey, H. A.; Holtzman, M. J.; Sheller, J. R.; Nadel, J. A. (1980) Bronchial hyperreactivity. Am. Rev. Respir. Dis. 121: 389-413.

Chaney, S.; Blomquist, W.; Muller, K.; DeWitt, P. (1980a) Biochemical effects of sulfuric acid mist inhalation by human subjects while at rest. Arch. Environ. Health 35: 270-275.

Chaney, S.; Blomquist, W.; Muller, K.; Goldstein, G. (1980b) Biochemical changes in humans upon exposure to sulfuric acid aerosol and exercise. Arch. Environ. Health 35: 211-216.

Fine, J. M.; Gordon, T.; Thompson, J. E.; Sheppard, D. (1987) The role of titratable acidity in acid aerosol-induced bronchoconstriction. Am. Rev. Respir. Dis. 135: 826-830.

Folinsbee, L. J. (1988) Human health effects of exposure to airborne acid. EHP Environ. Health Perspect.: in press.

Hackney, J. D.; Linn, W. S.; Avol, E. L. (1986) Controlled exposures of human volunteers to particulate pollution: recent findings and current research questions. In: Lee, S. D.; Schneider, T.; Grant., L. D.; Verkerk, P. J. eds. Aerosols: research, risk assessment, and control strategies: proceedings of the second U. S.-Dutch international symposium on aerosols; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 699-701.

Hackney, J. D.; Linn, W. S.; Avol, E. L. (1988) Acid fog: effects on respiratory function and symptoms in healthy and asthmatic volunteers. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Horstman, D.; Hazucha, M.; Haak, E.; Stacy, R. (1982) Effects of submicronic sulfuric acid aerosol on human pulmonary function. Arch. Environ. Health 37: 136-141.

Horstman, D. H.; Kehrl, H.; Weinberg, P.; Roger, L. J. (1986) Pulmonary function changes for asthmatics performing exercise while exposed to combined sulfur dioxide and sulfuric acid: an interim report. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment, and control strategies: proceedings of the second U.S.-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 703-709.

Horvath, S. M.; Folinsbee, L. J.; Bedi, J. F. (1982) Effects of large (0.9 um) sulfuric acid aerosols on human pulmonary function. Environ. Res. 28: 123-130.

Horvath, S. M.; Folinsbee, L. J.; Bedi, J. F. (1987) Combined effect of ozone and sulfuric acid on pulmonary function in man. Am. Ind. Hyg. Assoc. J. 48: 94-98.

Kagawa, J. (1986) Experimental studies on human health effects of aerosol and gaseous pollutants. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment, and control strategies: proceedings of the second U. S.-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 683-697.

Kerr, H. D.; Kulle, T. J.; Farrell, B. P.; Sauder, L. R.; Young, J. L.; Swift, D. L.; Borushok, R. M. (1981) Effects of sulfuric acid aerosol on pulmonary function in human subjects: an environmental chamber study. Environ. Res. 26: 42-50.

Kleinman, M. T.; Linn, W. S.; Bailey, R. M.; Jones, M. P.; Hackney, J. D. (1980) Effect of ammonium nitrate aerosol on human respiratory function and symptoms. Environ. Res. 21: 317-326.

Kleinman, M. T.; Bailey, R. M.; Chang, Y.-T. C.; Clark, K. W.; Jones, M. P.; Linn, W. S.; Hackney, J. D. (1981a) Exposures of human volunteers to a controlled atmospheric mixture of ozone, sulfur dioxide and sulfuric acid. Am. Ind. Hyg. Assoc. J. 42: 61-69.

Kleinman, M. T.; Linn, W. S.; Bailey, R. M.; Anderson, K. R.; Whynot, J. D.; Medway, D. A.; Hackney, J. D. (1981b) Human exposure to ferric sulfate aerosol: effects on pulmonary function and respiratory symptoms. Am. Ind. Hyg. Assoc. J. 42: 298-304.

Kleinman, M. T.; Bailey, R. M.; Whynot, J. D.; Anderson, K. R.; Linn, W. S.; Hackney, J. D. (1985) Controlled exposure to a mixture of SO_2, NO_2, and particulate air pollutants: Effect on human pulmonary function and respiratory symptoms. Arch. Environ. Health 40: 197-201.

Koenig, J. Q.; Pierson, W. E.; Horike, M.; Frank, R. (1982) Bronchoconstrictor responses to sulfur dioxide or sulfur dioxide plus sodium chloride droplets in allergic, nonasthmatic adolescents. J. Allergy Clin. Immunol. 69: 339-344.

Koenig, J. Q.; Pierson, W. E.; Horike, M. (1983) The effects of inhaled sulfuric acid on pulmonary function in adolescent asthmatics. Am. Rev. Respir. Dis. 128: 221-225.

Koenig, J. Q.; Morgan, M. S.; Horike, M.; Pierson, W. E. (1985) The effects of sulfur oxides on nasal and lung function in adolescents with extrinsic asthma. J. Allergy Clin. Immunol. 76: 813-818.

Koenig, J. Q.; Marshall, S. G.; Horike, M.; Shapiro, G. G.; Furukawa, C. T.; Bierman, W.; Pierson, W. E. (1987) The effects of albuterol on sulfur dioxide-induced bronchoconstriction in allergic adolescents. J. Allergy Clin. Immunol. 79: 54-58.

Kulle, T. J.; Kerr, H. D.; Farrell, B. P.; Sauder, L. R.; Bermel, M. S. (1982) Pulmonary function and bronchial reactivity in human subjects with exposure to ozone and respirable sulfuric acid aerosol. Am. Rev. Respir. Dis. 126: 996-1000.

Kulle, T. J.; Sauder, L. R.; Shanty, F.; Kerr, H. D.; Farrell, B. P.; Miller, W. R.; Milman, J. H. (1984) Sulfur dioxide and ammonium sulfate effects on pulmonary function and bronchial reactivity in human subjects. Am. Ind. Hyg. Assoc. J. 45: 156-161.

Kulle, T. J.; Sauder, L. R.; Hebel, J. R.; Miller, W. R.; Green, D. J.; Shanty, F. (1986) Pulmonary effects of sulfur dioxide and respirable carbon aerosol. Environ. Res. 41: 239-250.

Larson, T. V.; Covert, D. S.; Frank, R.; Charlson, R. J. (1977) Ammonia in the human airways: neutralization of inspired acid sulfate aerosols. Science (Washington, DC) 197: 161-163.

Leikauf, G.; Yeates, D. B.; Wales, K. A.; Spektor, D.; Albert, R. E.; Lippmann, M. (1981) Effects of sulfuric acid aerosol on respiratory mechanics and mucociliary particle clearance in healthy nonsmoking adults. Am. Ind. Hyg. Assoc. J. 42: 273-282.

Leikauf, G. D.; Spektor, D. M.; Albert, R. E.; Lippmann, M. (1984) Dose-dependent effects of submicrometer sulfuric acid aerosol on particle clearance from ciliated human lung airways. Am. Ind. Hyg. Assoc. J. 45: 285-292.

Linn, W. S.; Kleinman, M. T.; Bailey, R. M.; Medway, D. A.; Spier, C. E.; Whynot, J. D.; Anderson, K. R.; Hackney, J. D. (1981) Human respiratory responses to an aerosol containing zinc ammonium sulfate. Environ. Res. 25: 404-414.

Linn, W. S.; Avol, E. L.; Shamoo, D. A.; Whynot, J. D.; Anderson, K. R.; Hackney, J. D. (1986) Respiratory responses of exercising asthmatic volunteers exposed to sulfuric acid aerosol. J. Air Pollut. Control Assoc. 36: 1323-1328.

Lippmann, M. (1985) Airborne acidity: estimates of exposure and human health effects. EHP Environ. Health Perspect. 63: 63-70.

Lippman, M.; Albert, R. E.; Yeates, D. B.; Wales, K.; Leikauf, G. (1980) Factors affecting tracheobronchial mucociliary transport. In: Walton, W. H., ed. Inhaled particles IV: v. 1. Oxford, United Kingdom: Pergamon Press; pp. 305-319.

Lippmann, M.; Schlesinger, R. B.; Leikauf, G.; Spektor, D.; Albert, R. E. (1982) Effects of sulphuric acid aerosols on respiratory tract airways. In: Walton, W. H., ed. Inhaled particles V: proceedings of an international symposium organized by the British Occupational Hygiene Association; September 1980; Cardiff, United Kingdom; Ann. Occup. Hyg. 26: 677-690.

Newhouse, M. T.; Dolovich, M.; Obminski, G.; Wolff, R. K. (1978) Effect of TLV levels of SO_2 and H_2SO_4 on bronchial clearance in exercising man. Arch. Environ. Health 33: 24-32.

Sackner, M. A.; Ford, D.; Fernandez, R.; Cipley, J.; Perez, D.; Kwoka, M.; Reinhart, M.; Michaelson, E. D.; Schreck, R.; Wanner, A. (1978) Effects of sulfuric acid aerosol on cardiopulmonary function of dogs, sheep, and humans. Am. Rev. Respir. Dis. 118: 497-510.

Sackner, M. A.; Dougherty, R. D.; Chapman, G. A.; Zarzecki, S.; Zarzemski, L.; Schreck, R. (1979) Effects of sodium nitrate aerosol on cardiopulmonary function of dogs, sheep, and man. Environ. Res. 18: 421-436.

Schlesinger, R. B. (1985) Effects of inhaled acids on respiratory tract defense mechanisms. EHP Environ. Health Perspect. 63: 25-38.

Sim, V. M.; Pattle, R. E. (1957) Effect of possible smog irritants on human subjects. JAMA J. Am. Med. Assoc. 165: 1908-1913.

Spektor, D. M.; Leikauf, G. D.; Albert, R. E.; Lippmann, M. (1985) Effects of submicrometer sulfuric acid aerosols on mucociliary transport and respiratory mechanics in asymptomatic asthmatics. Environ. Res. 37: 174-191.

Spektor, D. M.; Yen, B. M.; Lippman, M. (1988) Effect of concentration and cumulative exposure of inhaled sulfuric acid on tracheobronchial particle clearance in healthy humans. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Stacy, R. W.; Seal, E., Jr.; House, D. E.; Green, J.; Roger, L. J.; Raggio, L. (1983) A survey of effects of gaseous and aerosol pollutants on pulmonary function of normal males. Arch. Environ. Health 38: 104-115.

Utell, M. J.; Morrow, P. E. (1986) Effects of inhaled acid aerosols on human lung function: studies in normal and asthmatic subjects. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment and control strategies: proceedings of the second U. S.-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 671-681.

Utell, M. J.; Swinburne, A. J.; Hyde, R. W.; Speers, D. M.; Gibb, F. R.; Morrow, P. E. (1979) Airway reactivity to nitrates in normal and mild asthmatic subjects. J. Appl. Physiol. 46: 189-196.

Utell, M. J.; Aquilina, A. T.; Hall, W. J.; Speers, D. M.; Douglas, R. G., Jr.; Gibb, F. R.; Morrow, P. E.; Hyde, R. W. (1980) Development of airway reactivity to nitrates in subjects with influenza. Am. Rev. Respir. Dis. 121: 233-241.

Utell, M. J.; Morrow, P. E.; Hyde, R. W. (1982) Comparison of normal and asthmatic subjects' responses to sulphate pollutant aerosols. In: Walton, W. H., ed. Inhaled particles V: proceedings of an international symposium organized by the British Occupational Hygiene Association; September 1980; Cardiff, United Kingdom; Ann. Occup. Hyg. 26: 691-697.

Utell, M. J.; Morrow, P. E.; Speers, D. M.; Darling, J.; Hyde, R. W. (1983) Airway responses to sulfate and sulfuric acid aerosols in asthmatics: an exposure-response relationship. Am. Rev. Respir. Dis. 128: 444-450.

Utell, M. J.; Morrow, P. E.; Hyde, R. W. (1984) Airway reactivity to sulfate and sulfuric acid aerosols in normal and asthmatic subjects. J. Air Pollut. Control Assoc. 34: 931-935.

Utell, M. J.; Morrow, P. E.; Hyde, R. W. (1985) Latent development of airway hyperreactivity in human subjects after sulfuric acid aerosol exposure. J. Aerosol Sci. 14: 202-205.

Utell, M. J.; Morrow, P. E.; Bauer, M. A.; Hyde, R. W.; Schrek, R. M. (1986) Modifiers of responses to sulfuric acid aerosols in asthmatics. In: Aerosols: formation and reactivity. London: Pergamon Press.

Utell, M. J.; Morrow, P. E.; Hyde, R. W.; Cox, C.; Schrek, R. M. (1987) Comparison of responses and deposition following human exposure via oral or nasal inhalation of sulfuric acid aerosols. Ann. Occup. Hyg.: in press.

Witek, T. J., Jr.; Schachter, E. N.; Beck, G. J.; Cain, W. S.; Colice, G.; Leaderer, B. P. (1985) Respiratory symptoms associated with sulfur dioxide exposure. Int. Arch. Occup. Environ. Health 55: 179-183.

6. EPIDEMIOLOGY STUDIES OF HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO ACID AEROSOLS

6.1 INTRODUCTION

To date, no epidemiological studies have directly demonstrated health effects to be associated with measured elevated ambient acid concentrations. This sparsity of data is due in part to the absence of adequate ambient acid measurement techniques until recent years and, conceivably, also to the current relatively low levels of ambient acid aerosols in many areas. Nevertheless, some evidence exists which is suggestive of human health effects being associated with exposures to ambient acid aerosols both (1) as derived from reexamination of older, historically important data on air pollution episode events in the U.S. and Europe and (2) as can be deduced from certain recent epidemiology studies carried out in the U.S., Canada, and Europe. This chapter concisely reviews such evidence first as it relates to acute exposure effects and then as it pertains to chronic exposure effects.

Because of the sparsity of concrete evidence, most of this chapter is devoted to identifying studies of situations in which there is good reason to suspect that high ambient acid concentrations existed in the evaluated study areas. From these studies the nature of the observed health effects are summarized as a basis for drawing tentative conclusions and suggesting directions for future research. However, no clear quantitative relationships are delineated because of the lack of sufficient ambient acid measurements by which to define exposure-response effects levels. Hopefully, several continuing studies currently underway in Canada, the United States, and Europe may provide useful information in the near future. These face the difficult task of separating out effects due to relative contributions of various air pollutants present (e.g., differentiating between O_3 effects and between those of H^+). The extremely critical need for extensive additional research becomes obvious as a consequence of the present examination of currently available information.

6.2 ACUTE EFFECTS STUDIES

6.2.1 Acute Episode Studies

Some of the earliest indications that ambient air acid aerosols may be associated with human health effects can be discerned upon reexamination of historically important air pollution episode events. These include, for example, the Meuse Valley (Belgium), Donora, PA (USA), and well-known London (UK) episodes, as discussed below.

6.2.1.1 Meuse Valley. Firket (1931) describes the fogs of December 1930 in the Meuse Valley and the morbidity and mortality related to them. A detailed discussion of the causes is presented which concludes that the main component of the fog that caused the health effects that occurred was sulfuric acid. This conclusion was based both upon consideration of the emissions in the valley, the weather conditions and the aerometric chemistry required for the production of sulfuric acid. Additionally, the pathophysiology seen was thought to relate to sulfuric acid exposure more so than to other possible agents. More than 60 persons died from this acid fog and several hundred suffered respiratory problems, with a large number becoming complicated with cardiovascular insufficiency. The mortality rate during the fog was over ten times higher than the normal rate. Those persons especially affected by the fog were the elderly, those suffering from asthma, heart patients and the debilitated. Most children were not allowed outside during the fog and few attended school. Unfortunately, no actual measurements of acid aerosols in ambient air during the episode are available by which to establish clearly their role in producing the observed health effects versus the relative contributions of other specific pollutants.

6.2.1.2 Donora. Schrenk et al. (1949) reported on the health effects and atmospheric pollutants of the smog episode in Donora of October 1948. A total of 5,910 persons (or 42.7 percent) of the total population of Donora experienced some effect from the smog. The air pollutant-ladened fog lasted from the 28th to the 30th of October, and during a 2-week period 20 deaths took place, 18 of them being attributed to the fog. An extensive investigation by the American Public Health Service concluded that the health effects observed were mainly due to an irritation of the respiratory tract. Mild upper respiratory tract symptoms were evenly distributed through all age groups and, on the average, were of less than four days duration. Cough was the most predominant symptom; it occurred in one-third of the population and was evenly distributed through all age groups. Dyspnea was the most frequent symptom in the more severely affected, being reported by 13 percent of the population, with a steep rise as age progressed to 55 years; above this age, more than half of the persons affected complained of dyspnea.

It seems reasonable to state that, while no single substance can be clearly identified as being responsible for the October 1948 episode, the observed health effects syndrome could have likely been produced by two or more of the contaminants, i.e., sulfur dioxide and its oxidation products together with particulate matter, as among the more significant contaminants present. Hemeon (1955) examined the water soluble fraction of solids on a filter of an electronic air cleaner operating during the smog in Donora and concluded that acid salts were an important component.

6.2.1.3 London Acid Aerosol Fogs. Based on the mortality rate in the Meuse Valley, Firket (1931) estimated that 3,179 sudden deaths would likely occur if a pollutant fog similar to that in the Meuse Valley occurred in London. An estimated 4,000 deaths did later indeed occur during the London Fog of 1952, as noted by Martin (1964). During the fog of 1952, evidence of bronchial irritation, dyspnea, bronchospasm and, in some cases, cyanosis is clear from hospital records and from the reports of general practitioners. There was a considerable increase in sudden deaths from respiratory and cardiovascular conditions. The nature of these sudden deaths remains a matter for speculation since no specific cause was found at autopsy. Evidence of irritation of the respiratory tract was, however, frequently found and it is not unreasonable to suppose that acute anoxia due either to bronchospasm or exudate in the respiratory tract was an important factor. Also, the United Kingdom Ministry of Health (1954) reported that in the presence of moisture, aided perhaps by the surface activity of minute solid particles in fog, some sulfur dioxide is oxidized to trioxide. It is probable, therefore, that sulfur trioxide, dissolved as sulfuric acid in fog droplets, appreciably augmented the harmful effects of sulfur dioxide and/or other particulate matter species.

Martin and Bradley (1960) reported increases in daily total mortality among the elderly and persons with preexisting respiratory or cardiac disease in relation to SO_2 and PM (British Smoke; BS) levels in London during the winter of 1958-1959. The pathological findings in 12 fatal cases and the clinical evidence of practitioners seem to indicate clearly that the harmful effects of the fog were produced by the irritating action of polluted air drawn into the lungs. These effects were more obvious in people who already suffered from a chronic respiratory disease and whose bronchi were presumably more liable to bronchospasm.

Waller (1963) reported that sulfuric acid was one of the pollutants considered as a possible cause of the increased morbidity and mortality noted during the London fog of December 1952. Because of this, as noted earlier in Chapter 2, following the 1952 pollution episode daily measurements were made in London of BS and SO_2 levels starting in 1954 and, later, concentrations of sulfuric acid were calculated from net aerosol acidity or actually measured during air pollution episodes on a daily basis starting in 1964. No regular measurements of sulfuric acid were made during the winter of 1955-1956 but some was detected at times of high pollution. For example, Waller and Lawther (1957) detected the presence of acid droplets in samples collected in January of 1956. Insufficient measurements were made, however, during the rest of the winter of 1955-1956 to study the effects of the acid aerosol present. Waller (1963) later reported measuring acid droplets in London in the winter of 1958-1959 with mass median diameter of 0.5 μm. Commins (1963) measured particulate acid in the city of London and found concentrations especially high at times of fog reaching levels of 678 μg (calculated as sulfuric acid)/m^3 of air. Typical winter daily concentrations were 18 μg/m^3 compared to 7 μg/m^3 in the summer. The sulfuric acid content of the air in the city of London at the time could range up to 10 percent of the total sulfur.

The concentration of sulfuric acid rises with that of smoke, and it may be partly responsible for health effects observed for chronic bronchitic patients in London during the late 50's and throughout the 60's. Since many patients become worse even at times of relatively low humidity, this suggests that small droplets of strong acid may have had more effect than larger ones. Lawther et al. (1970) reported an association between daily pollutant levels (BS and SO_2) and worsening of health status among a group of over 1,000 chronic bronchitis patients in London during the winters of 1959-1960 and 1964-1965. A daily technique for self-assessment of day-to-day change in health status was used. An interesting study was also conducted on a smaller sample of the patients during in the winters of 1964-1965 and 1967-1968 when pollutant levels were somewhat lower than in earlier years. Approximately 50 subjects selected for their susceptibility to air pollutant effects formed the sample. Daily sulfuric acid, measured at St. Bartholomew Hospital Medical College, was reported as having a relatively high correlation with health effects in the 1964-1965 winter. For 1967-1968, all these correlation coefficients were lower but still significant. The authors comment that the patients selected must have been particularly sensitive to pollution, since from past experience no correlation would have been expected with such very low levels of pollution encountered by such a small group.

Relationships between London air pollution levels and mortality have been extensively reexamined during recent years, using more sophisticated statistical analyses techniques, e.g., time-series analyses and various "filtering" approaches to deal with potential confounding by extraneous cyclical factors. Several authors (Mazumdar et al., 1982; Ostro, 1984; Schwartz and Marcus, 1986) have reported significant associations between BS and SO_2 levels and mortality during 14 London winters (1958-72), with associations of mortality with BS being much stronger than with SO_2 at levels below 500 $\mu g/m^3$. Thurston et al. (1988) have also presented a preliminary report on reanalyses for those portions of the 1958-1972 London mortality data for which daily direct acid aerosol measurements were made at St. Bartholomew's Medical College (see Chapter 2, Section 2.5.1). The authors found that acid aerosol concentrations were more strongly associated with unadjusted total mortality than were BS or SO_2. This was in spite of the fact that seven sites were used for the BS and SO_2 measurements versus one site for the acid aerosols. The authors also found that lags of one day provided better fits for the pollution variables than did the same day variables. Additional analyses using models that involve more sophisticated time series methods are in progress and are needed in order to provide more definitive confirmation of acid aerosol contributions to London mortality.

In summary, the early historically important air pollution data discussed above provide some limited evidence for mortality and morbidity effects being associated with ambient air concentrations of acid aerosols. The calculations and measurements of sulfuric acid levels (estimated to range up to 678 $\mu g/m^3$) during some London episodes in the late fifties provide plausible bases for hypothesizing contributions of sulfuric acid aerosols to the health effects observed during those episodes. The recent preliminary analyses by Thurston et al. (1988) of daily direct acid aerosol measurements over a longer span of time (1958-1972) in London are especially important in providing more direct evidence for likely associations between ambient acid aerosols and mortality.

6.2.2 European Acid Event of 1985

In addition to evidence derived from the above historically important data, indications of possible involvement of ambient acid aerosols in the induction of human health effects can be discerned through recent analyses of a 1985 European air pollution episode. During January 1985, large parts of Europe from western Germany to Great Britain experienced a pollution event. This event was tracked by monitoring stations in several countries as it moved from east to west, and then finally dissipated over the North Sea. Unfortunately, very few measurements of ambient acidity are available. Only the data of de Leeuw and van Rheineck Leyssius (1988) suggest that sulfuric and nitric acid levels exceeded 50 $\mu g/m^3$ during these periods.

Wichmann et al. (1988) studied mortality, hospital admissions, ambulance transports and outpatient visits for respiratory and cardiovascular disease in West Germany during the 1985 event. During this time, daily suspended particulates reached 600 $\mu g/m^3$, SO_2 reached 830 $\mu g/m^3$, and NO_2 reached 410 $\mu g/m^3$. Total mortality rose immediately with the increase in pollution (January 16, 1985), and reached a maximum on January 18. The increase in mortality was about 8 percent. Similarly, increases in hospital admissions (15 percent), outpatient visits (12 percent), and ambulance transports (28 percent) were seen.

The progress of the event was monitored by de Leeuw and van Rheineck Leyssius (1988) as it passed through the Netherlands. The event started on January 15 and ended on January 21, 1985. The SO_2 levels peaked at 280 $\mu g/m^3$ on January 20, 1985. No actual acid measurements were presented for the event itself. Dassen et al. (1986) measured pulmonary function in primary school children before, during, and after the event. The authors found that pulmonary function indices were significantly lower by 3 to 5 percent when compared to baseline values taken 4 to 6 weeks earlier. The decrements were still present 16 days later, but not 25 days later.

Ayres et al. (1988) studied respiratory morbidity in patients of general practitioners in England during the same period. Although acute bronchitis rates were elevated for children aged 14 or less during the third week of January, 1985, the rates during this period were also elevated in other years because of the immediately preceding holiday period. As a result, no clear conclusions could be drawn from the British data that relate health effects to the January 1985 episode.

Collectively the above analyses are indicative of notable increased health effects occurring in several countries during the 1985 European episode. Certain of the analyses, Wichmann et al. (1988) and Dassen et al. (1986), appear to provide clear linkages between the observed health effects and measured air pollutants (e.g., PM, SO_2). The presence of elevated acidic species (sulfuric and nitric acid) in the polluted air mass makes it plausible that acid aerosols may have contributed to the observed health effects, but the sparsity of actual acid measurements during and after the event makes it difficult to evaluate their potential role. If they were involved, then acid levels ranging up to 50 $\mu g/m^3$ or more would likely be implicated.

6.2.3 Acute Exposure Studies of Children

Several studies have recently been carried out in the United States and Canada that examine the effects of exposures to air pollutants on pulmonary function in children at summer camps. Some of the available data derived from these studies allow evaluation of possible involvement of acid aerosols in the health effects observed.

Lippmann et al. (1983) studied 83 nonsmoking, middle class, healthy children (ages 8 to 13) during a 1980 2-week summer camp program in Indiana, PA. The children were involved in camp activities which resulted in their exercising outdoors most of the time. At least once, each child had height and weight measured and performed spirometry on an 8 liter Collins portable recording spirometer in the standing position without nose clip. During the study, peak flow rates were obtained by Mini-Wright® peak flow meter at the beginning of the day or at lunch and adjusted for both age and height. Ambient air levels of TSP, hydrogen ions, and sulfates were monitored by a high-volume sampler on the rooftop of the day camp building. Ozone levels were estimated using a model that used ozone data from monitoring sites located 32 and 100 km away. The hi-vol samples were collected on H_2SO_4 treated quartz fiber filters for the determination of the concentration of H+ and total suspended particulate matter (TSP). H+ was determined from filter extract using a Gran titration. Peaks in acid concentration occurred on four days, when the acid values ranged between 4 and 6.3 $\mu g/m^3$ (as H_2SO_4). On many occasions there was no H_2SO_4 in the atmosphere. While effects were reported as being significantly associated with exposure to ozone, no effects were found to be related to exposure to H_2SO_4 at the acid levels observed during the study.

Bock et al. (1985) and Lioy et al. (1985) examined pulmonary function of 39 children at a camp in Mendham, New Jersey during a 5-week period in July-August, 1982. Ozone was continuously monitored using chemiluminescent analysis. Ambient aerosol samples were collected on Teflon filters with a dichotomous sampler having a 15 µm fractionation inlet and a coarse/fine cut-size of 2.5 µm (Sierra Mod 244-E). Aerosol acidity as measured by strong acid (H+) content, was determined using the pH method. Highly significant changes in peak expiratory flow rate (PEFR) were found to be related to ozone exposure, as well as a baseline shift in PEFR lasting approximately one week following a haze episode in which the O_3 exposure exceeded the NAAQS for four consecutive days that included a maximum concentration of 185 ppb. There was no apparent effect of H+ on pulmonary function. The authors did state, however, that the persistent effects associated with the ozone episode could have been due to acid sulfates as well as, or in addition to, ozone but additional uncollected data were needed to evaluate this possibility.

During a four-week period in 1984, Lioy et al. (1987) and Spektor et al. (1988a) measured respiratory function of 91 active children who were residing at a summer camp on Fairview Lake in northwestern New Jersey. Continuous data were collected for ambient temperature, humidity, wind speed and direction, and concentrations of O_3, H_2SO_4, and total sulfates. Ozone was measured by U.V. absorbance, and H_2SO_4 and total sulfates were alternately determined by a flame photometric sulfate analyzer (Meloy Model 285) preceded by a programmed thermal pretreatment unit. The ambient aerosol samples were collected on quartz fiber filters with a dichotomous sampler having a 15 µm fractionating inlet (PM_{15}) and a coarse/fine cut-size of 2.5 µm (Sierra Model 244-E). Aerosol acidity, as measured by strong acid (H+) content, was determined using the pH method. The maximum values recorded for H_2SO_4 and NH_4HSO_4 were 4 and 20 $\mu g/m^3$ respectively. While effects were reported as being associated with exposure to ozone, no effects were found to be related to exposure to the moderate acid aerosol concentrations experienced in this study.

Raizenne et al. (1987a) studied possible relationships between respiratory function parameters and environmental factors at Camp Kiawa, Ontario, Canada during the summer of 1986. Twelve young females (9 to 14 years old) at a residential summer camp for girl guides performed pre- and post-exercise spirometry on a day of low air pollution and at the peak of an air pollution episode. Clinical interviews, atopy, and methacholine airway hyperresponsiveness tests were performed at the camp on the first 2 days of the study. Seven subjects had positive responses to methacholine challenge (+MC) and five did not (-MC). A standardized ergometric physical capacity test was also administered, in which minute volume, heart rates, and total work achieved were recorded. Air monitoring was performed on site and, during the episode, air pollution concentrations were: O_3 exceeded 130 ppb; H_2SO_4 exceeded 40 $\mu g/m^3$; total sulfate exceeded 80 $\mu g/m^3$. Additional discussion of the aerometric monitoring is given by Spengler et al. (1988). Lung function responses were modelled by multivariate normal methods on the indicator of airway hyperresponsiveness. For the entire group (N = 12), post exercise FVC and FEV_1 were observed to increase on the control day and decrease on the episode day. On the control day, an average 40 mL increase in FVC due to exercise was observed ($p < .05$) for the whole group, with a 71 mL increase in -MC subjects and a 17 mL increase in +MC subjects. Although not statistically significant at the 10 percent level, mean FVC for the entire group was 30 mL less on the day of high pollution versus low pollution, and this difference was more pronounced in -MC (-65 mL) than +MC (-4 mL) subjects. The effect of exercise in the model was statistically significant ($p < .05$), whereas the pollution day effect was not. These results suggest that lung function responses to exercise differ in +MC and -MC subjects under field research conditions and that the expected normal FVC response to exercise in both groups is altered during periods of elevated ambient pollution. However, no analyses were presented that evaluated possible acid aerosol relationships to health effects.

Raizenne et al. (1987b) also studied 112 young girls who participated in one of three two-week camp sessions at Camp Kiawa, Ontario, Canada during June to August, 1986. A self-administered questionnaire was completed by a parent before the camp; daily spirometry was taken between 3:00 and 5:00 p.m. during the camp; and methacholine bronchial challenge testing was completed on day 3 or 4 of the camp. During the study, air pollutant monitoring was performed for ozone, sulfur dioxide, nitrogen oxides, particulate matter, pH, and sulfuric acid. Raizenne et al. (1987b) indicate that analyses of possible air pollutant effects are being carried out by using regression analyses to estimate separate slopes for pulmonary function parameters for each child, but the results are not yet available.

Raizenne et al. (1988) examined acute lung function response in the 112 subjects at Camp Kiawa in relation to four ambient acid aerosol events (the highest H_2SO_4 level was 47.7 $\mu g/m^3$ during one event on July 25, 1986). The influence of air pollution on lung function was evaluated first by comparing responses on the day of a pollutant event (high acid and ozone levels) to the mean of the responses on corresponding control days of low pollutant levels. For FEV_1, there was a tendency for the lung function decrements on the event day to be greater than the response on the corresponding control days, except for the last event (when an increase in function was observed). The largest decrements for FEV_1 and PEF (48-66 mL decline for FEV_1) were observed on the morning after the highest H_2SO_4 event on July 25, 1986. No analyses were presented, however, that attempted to separate out pollutant effects of H_2SO_4 from those of O_3.

Airway hyperresponsiveness using a methacholine bronchoconstriction provocation test, was assessed for 96 of the subjects in the Raizenne et al. (1988) study. Children with a positive response to methacholine challenge had larger decrements compared to their nonresponsive counterparts. These preliminary results do not allow definitive statements to be made on the susceptibility of methacholine sensitive subjects; however, there are indications in these data of differential lung function profiles and responses to air pollutants in children with and without airway hyperresponsiveness. Further analyses and research are indicated.

Franklin et al. (1985) and Raizenne et al. (1987b) reported preliminary analyses on data from another study in Canada. In 1983, fifty-two campers (23 were asthmatics) at the Lake Couchiching Summer Camp, Ontario were studied to examine lung function performance in relation to daily pollutant concentrations. The health assessment included a precamp clinical evaluation, a telephone administered questionnaire on respiratory health, daily symptomatology questionnaire, assessments of activity level, and twice daily lung function measurements. Pollutants measured included O_3, respirable particles, sulfates, NO_2, and SO_2. Respirable sulfates were highly variable and ranged from 10 to 26 $\mu g/m^3$. Sulfate as sulfuric acid was usually very low. Preliminary analyses suggest that minimal, if any, acute health effects can be attributed directly to the air pollutants monitored. Raizenne et al. (1986) report further analyses showing that, for individual pollutants, a time lag function for fine particles, average sulfate concentrations, maximum daily O_3 levels and temperature were all associated with decrements in specific lung function indices. Further analyses are still underway or not yet published. Pollutant specific data were not discussed in Raizenne et al. (1986). Although the results are suggestive of a short-term pollutant effect on lung function, details of the actual pollutant levels were not given. The weightings given to each specific pollutant were also not given, but are critical for adequate evaluation of the study.

It is of interest to compare results obtained between the above summer camp studies and in relation to findings of certain controlled human exposure studies or other epidemiology studies. For example, Spengler et al. (1988) calculated that the children in the Raizenne et al. (1988) study received an average one-hour respiratory tract dose of 1,050 nmoles of H^+ ions, based on an exposure model which takes into account not only the concentration of exposure but also minute ventilation rate. Spengler et al. (1988) further noted that the asthmatic subjects in the human clinical studies of Utell et al. (1983) and Koenig et al. (1983) had experienced an airway dose of approximately 1,200 nmoles of H^+, which evoked a response at reported concentrations of 450 $\mu g/m^3$ and 100 $\mu g/m^3$ H_2SO_4 respectively. These calculations suggest that, because of differences in minute ventilation rates, the peak levels occurring at Camp Kiawa during an ambient acid aerosol event may have produced exposures similar to those seen in clinical studies of asthmatic subjects. It remains to be determined as to what extent comparable C x T total respiratory tract dose(s) for H^+ ions may be effective in producing pulmonary function decrements beyond the short exposure times employed in the controlled human exposure studies or in producing other types of effects. For example, Spektor et al. (1988b) found that the effect of doubling the length of exposure to sulfuric acid increased average tracheobronchial clearance half-time from 100 to 162 percent relative to control.

6.2.4 Acute Studies Relating Health Effects to Sulfates

Sulfate and nitrate levels may represent crude surrogates for potential acid aerosol levels; however, the appropriateness of use of sulfate and/or nitrate concentrations as indices of exposure to acid aerosols has not yet been well evaluated. In Section 2.4.2 it was indicated that sulfate species represent the principal component of most acid aerosols. The problem is that measurements of total sulfate and/or nitrate levels may not only represent acid aerosol exposures but sulfate/nitrate exposures that are not acidic as well. Thus, the studies discussed below which present sulfate and/or nitrate data but not acid aerosol data may provide only limited insight into the potential health effects that may be related to acid aerosol exposure.

Bates and Sizto (1983, 1986) reported results of an ongoing correlational study relating hospital admissions in southern Ontario to air pollutant levels. Data for 1974, 1976, 1977, and 1978 were discussed in the 1983 paper. The 1986 analyses evaluated data up to 1982 and showed: (1) no relationship between respiratory admissions and SO_2 or COHs in the winter; (2) a complex relationship between asthma admissions and temperature in the winter; and (3) a consistent relationship between respiratory (both asthma and nonasthma) admissions in summer and sulfate and ozone concentrations, but not to summer COH levels. However, Bates and Sizto note that the data analyses are complicated by long-term trends in respiratory disease admissions unlikely related to air pollution, but they nevertheless hypothesize that observed effects may be due to a mixture of oxidant and reducing pollutants which produce intensely irritating gases or aerosols in the summer but not in the winter.

Bates and Sizto (1987) later studied admissions to all 79 acute-care hospitals in Southern Ontario, Canada (i.e., the whole catchment area of 5.9 million people) for the months of January, February, July and August for 1974 and for 1976 to 1983. Air pollution data for O_3, NO_3, SO_2, coefficient of haze (COH), and aerosol sulfates were obtained from 17 stations between Windsor and Peterborough. Total admissions and total respiratory admissions declined about 15 percent over the course of the study period, but asthma admissions appeared to have risen. Evaluating the asthma category of admissions is complicated by the effects of a change in International Classification of Disease (ICD) coding in 1979. The analyses demonstrate that there is a consistent summer relationship between (1) sulfates, ozone and temperature and (2) respiratory admissions with or without asthma. This conclusion is strengthened by the continuing lack of any association of these variables with non-respiratory conditions. The present data raise the question of whether the association of increased respiratory admissions in the summer in this region can be associated with ozone or sulfates. It would be surprising for the effects to be related to ozone since it is aerosol sulfates that, in summer, explain the highest percentage of the variance in respiratory admissions; yet these are not correlated with respiratory admissions in the winter. In view of this, the possibility exists that the observed health effects might be attributable neither to ozone nor to sulfates, but to some other air pollutant species that "travel" with them over the region in the summer (but not in the winter).

Bates and Sizto (1987) note that recent observations suggest the presence of unusual peaks of H+ aerosol of small particle size in this region of Canada in the summer, concomitant with elevated O_3 and $SO_4^=$ levels. On two days in July 1986 in Eastern Toronto when ozone and sulfate levels were elevated, but not higher than on other days, peaks of H+ acid aerosol lasting for up to two hours were recorded at levels of 10 to 15 $\mu g/m^3$. The particle size was small (about 0.2 μm). Similar observations were recorded on the same days by another H+ air sample operation west of Toronto. This raises the possibility that the types of health effects noted above might be attributable neither to ozone, nor to sulfates but rather perhaps to acid aerosols.

The evidence from Bates and Sitzo (1983, 1986, 1987, 1988) neither conclusively relates sulfates nor ozone to hospital admissions. Instead, the results suggest that some other pollutant(s) may be responsible, e.g., sulfuric acid that has been measured in the region. More aerometric data will be required, however, to confirm or disprove this possibility, and a new study is underway to examine these factors.

6.3 CHRONIC EXPOSURE EFFECTS STUDIES

As was the case for acute exposure effects, only very limited epidemiologic study data currently exist by which to attempt to evaluate possible relationships between chronic exposures to ambient acid aerosols and human health effects. These include one study from Japan relating effects to estimated or measured acidity and several other North American studies, which relate effects to sulfate levels or other surrogate measures thought to roughly parallel acid aerosol concentrations.

6.3.1 Acid Mists Exposure In Japan

Kitagawa (1984) examined the cause of the Yokkaichi asthma events (1960 to 1969) by examining the potential for exposure to concentrated sulfuric acid mists and the location and type of health effects noted. He concluded that the observed respiratory diseases were due not to sulfur dioxide but to concentrated sulfuric acid mists emitted from stacks of calciners of a titanium oxide manufacturing plant located windward of the residential area. This was based on the fact that the SO_3/SO_2 ratio of 0.48 was much higher than the normal range of 0.02 to 0.05. The higher ratio indicates a higher acid aerosol level. The acid particles were fairly large (0.7 to 3.3 μm) compared with acid aerosols seen in the United States of America (see Chapter 2). More than six hundred patients with respiratory disease were found between 1960 and 1969 with chronic bronchitis, allergic asthmatic bronchitis, pulmonary emphysema and sore throat. In 1969, measures of acid aerosol exposures were obtained from litmus paper measurements collected near the industrial plant which showed that acid mist particles were distributed leeward of the industrial plant. The author notes that the physiological effects of concentrated sulfuric acid mists must be quite different from that of dilute sulfuric acid mists formed by atmospheric oxidation of sulfur dioxide, and that the distinction between the two types of acid mists is very important.

6.3.2 Chronic Studies Relating Health Effects to Sulfates

Franklin et al. (1985) described a Canadian cross sectional study done in fall, 1983 and winter, 1984, which examined potential chronic health effects of exposure to pollutants in 7- to 12-year-old children. Health indices used included an initial self-administered health questionnaire, biweekly health diaries done through telephone interviews, and pulmonary function tests. A control town, Portage la Prairie Manitoba, had lower pollutant levels than Tillsoburg, Ontario, the study community. Ambient pollution monitoring for SO_2, NO_2, PM_{10}, $SO_4^=$, and NO_3^- was performed in both towns. Preliminary analysis indicated that a difference (adjusted for the age, sex, and height of child) may exist between towns in several parameters related to pulmonary function. But caution was urged, because important confounding factors had not yet been considered. Later, Raizenne et al. (1987b) reported that of the 1,414 children studied, 81 percent provided sufficient questionnaire data and produced acceptable pulmonary function tests for proper analysis.

The results indicate that residence in the polluted region was significantly associated with pulmonary decrements of 2.2 percent for FVC and 1.7 percent for $FEV_{1.0}$. Although not statistically significant, the reported incidence of chronic respiratory symptoms was higher in Tillsonburg compared to the control community. These results were not influenced by parental smoking, length of residence, cooking fuel, schools, indoor air pollution and subject morphometric data. Pollutant-specific analyses were not discussed, but further analyses are anticipated. The statistically significant differences in observed chronic respiratory symptom rates must be viewed with caution. The measurement itself is somewhat subjective and naturally has significant differences from one geographic area to another. The air pollutant concentrations observed were all quite low compared with comparable U.S. cities.

Ware et al. (1986) have reported results of analyses from the ongoing Harvard study of outdoor air pollution and respiratory health status of children in six eastern and midwestern U.S. cities. Between 1974 and 1977, approximately 10,100 white preadolescent children were enrolled in the study during three successive annual visits to the cities. On the first visit, each child underwent a spirometric examination, and a parent completed a standardized questionnaire regarding the child's health status and other important background information. Most of the children (8,380) were seen for a second evaluation one year later. Measurements of TSP, sulfate fraction, and SO_2 concentrations at study-affiliated outdoor stations were combined with data from other public and private monitoring sites to create a record of pollutant levels in each of nine air pollution regions during a one-year period preceding each evaluation, and for TSP during each child's lifetime up to the time of evaluation. TSP levels ranged from 32 to 163 $\mu g/m^3$ (annual average). SO_2 levels ranged from 2.9 to 184 $\mu g/m^3$, and sulfate levels ranged from 4.5 to 19.3 $\mu g/m^3$.

Analyzing data across all six cities, Ware et al. (1986) found that frequency of chronic cough was significantly associated ($p < 0.01$) with the average of 24-h mean concentrations of all three air pollutants during the year preceding the health examinations. Rates of bronchitis and a composite measure of lower respiratory illness were significantly ($p < 0.05$) associated with annual average particle concentrations. However, within the individual cities, temporal and spatial variation in air pollutant levels and symptom or illness rates were not significantly associated. The history of early childhood respiratory illness for lifetime residents was significantly associated with average TSP levels during the first two postnatal years within cities, but not between cities. Furthermore, pulmonary function parameters (FVC and FEV_1) were not associated with pollutant concentrations during the year immediately preceding the spirometry test or, for lifetime residents, with lifetime average concentrations. Ferris et al. (1986), however, reported a small effect on lower airway function (MMEF) related to fine particle concentrations. Spengler et al. (1986) report the occurrence of acid aerosol peak concentrations of 30 to 40 $\mu g/m^3$ in two of the cities during recent monitoring.

Overall, these results appear to suggest that risk may be increased for bronchitis and some other respiratory disorders in preadolescent children at moderately elevated levels of TSP, sulfate fraction, and SO_2 concentrations, which do not appear to be consistently associated with pulmonary function decrements. However, the lack of consistent significant associations between morbidity endpoints and air pollution variables within individual cities argues for caution in interpreting the present results.

In an hypothesis-generating discussion preceding a presentation of a new multicity study (see Section 6.5 and 8.4), Speizer (1988) presents city-specific bronchitis prevalence rates from four of the above six cities where H^+ concentrations were measured. While no direct aerosol acidity measurements were actually made during or before the 1980/81 school year (when the children were examined), Speizer (1988) utilized data that Spengler et al. (1988) gathered in Kingston/Harriman and St. Louis from December 1985 through September 1986 and in Steubenville and Portage from November 1986 to early September 1987. When the city-specific bronchitis rates are plotted against mean H^+ concentrations instead of PM_{15}, there is a relative shift in the ordering of the cities which suggest a better correlation of bronchitis prevalence with H^+ than with PM_{15} (see Figures 6-1 and 6-2). This qualitative information points toward the need for research evaluating the role acid aerosols may play in the development of bronchitis.

The potential role of acid aerosols in the development of bronchitis is suggested by the results of animal studies discussed in Chapter 4. Results from animal studies indicate that at low levels (250 $\mu g/m^3$), and with chronic exposure, the main response is hypertrophy and/or hyperplasia of mucus secretory cells in the respiratory epithelium; these alterations may extend to the small bronchi and bronchioles, where secretory cells are normally rare or absent. This could result in an increase in secretory rate and mucus volume in such airways which could be a possible factor in the pathogenesis of obstructive lung disease. But no study documents an actual increase in secretory rate or mucus volume. Although mucus hypersecretion is a characteristic of obstructive lung disease, particularly chronic bronchitis, respiratory epidemiologists

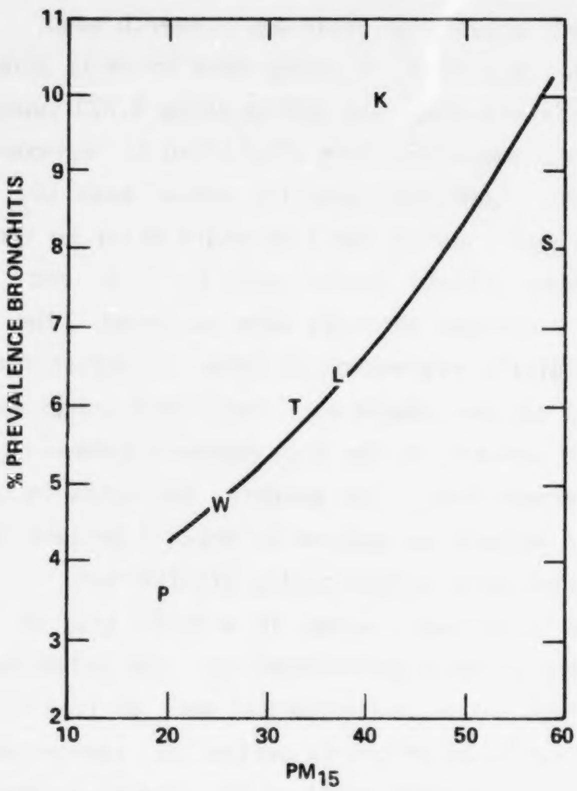

Figure 6-1. Bronchitis in the last year, children 10 to 12 years of age in six U.S. cities, by PM$_{15}$. (P = Portage, WI; T = Topeka, KS; W = Watertown, MA; K = Kingston, TN; L = St. Louis, MO; S = Steubenville, OH)

Source: Speizer (1988).

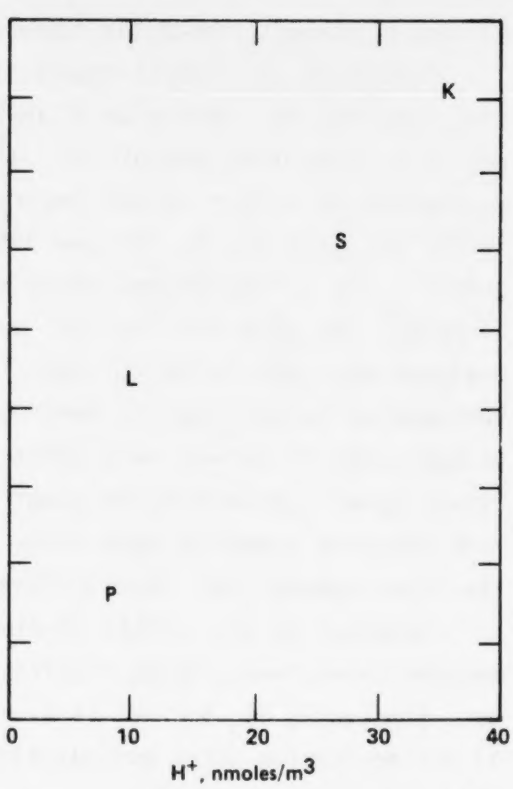

Figure 6-2. Bronchitis in the last year, children 10 to 12 years of age in four U.S. cities, by hydrogen ion concentrations. (K = Kingston, TN; L = St. Louis, MO; P = Portage, WI; S = Steubenville, OH)

Source: Speizer (1988).

have produced conflicting results regarding its importance in the development of obstructive lung disease. Annesi and Kauffmann (1986) concluded that the presence of chronic phlegm production was predictive of subsequent mortality based upon their study of 1, 061 men working in the Paris area followed for a period of 22 years. Peto et al. (1983) concluded that mucus hypersecretion is not a link in any important causal chain that accelerates the development of air-flow obstruction based upon their study of 2,718 British men in a 20 year follow-up study. Bates (1983) comments that the work of Peto and his colleagues (1983) add an important epidemiological perspective to the clinical and pathological observation supporting the thesis of probable dissociation between the development of chronic air flow limitations and mucus hypersecretion. Thus, new studies that may add to the data base on the natural history of chronic bronchitis represent a basic epidemiology research need.

Chapman et al. (1985) report the results of a survey done in early 1976 that measured the prevalence of persistent cough and phlegm among 5,623 young adults in four Utah communities. The communities were stratified to represent a gradient of sulfur oxides exposure. Community specific annual mean SO_2 levels had been 11, 18, 36, and 115 $\mu g/m^3$ during the five years prior to the survey. The corresponding annual mean sulfate levels were 5, 7, 8, and 14 $\mu g/m^3$. No gradients for TSP or suspended nitrates were observed. The analyses were made using multiple logistic regression in order to adjust for confounding factors such as smoking, age and education. Persistent cough and phlegm rates in fathers were about 8 percent in the high exposure community, versus about 3 percent in the other communities. For mothers, the rates in the high exposure community were about 4 percent as opposed to about 2 percent in the other communities. Both differences were statistically significant.

Schenker et al. (1983) studied 5,557 adult women in a rural area of western Pennsylvania using respiratory disease questionnaires. Air pollution data (including SO_2 but not particulate matter measurements) were derived from 17 air monitoring sites and stratified in an effort to define low, medium and high pollution areas. The four-year means (1975-1978) of SO_2 in each stratum were 62, 66, and 99 $\mu g/m^3$ respectively. Respiratory symptom rates were modeled using multiple logistic regression, which controlled for several potentially confounding factors, including smoking. A model was used to estimate air pollutant concentrations at population-weighted centroids of 36 study districts. The relative risk (odds ratio) of "wheeze most days or nights" in nonsmokers residing in the high and medium pollution areas was 1.58 and 1.26 ($p = 0.02$) respectively, as compared with the low pollution area. For residents living in the same location for at least five years, these relative risks were 1.95 and 1.40 ($p <0.01$). Also, the increased risk of grade 3 dyspnea in nonsmokers was associated with SO_2 levels at $p = <0.11$. However, no significant association was observed between cough or phlegm and air pollution variables. The results of this study suggest that wheezing may be associated with SO_2 levels, but these results must be viewed with caution since the gradient between areas was small and there were no particle or other pollutant measures. Lippmann (1985) suggested that it was plausible that the effects in this study are associated with submicrometer acid aerosol which deposits primarily in small airways, rather than with SO_2 levels.

Dodge et al. (1985) reported on a longitudinal study of children exposed to markedly different concentrations of SO_2 and moderately different levels of particulate sulfate in Southeastern U.S. towns. In the highest pollution area, the children were exposed to 3 hour peak SO_2 levels exceeding 2,500 $\mu g/m^3$ and annual mean particulate sulfate levels of 10.1 $\mu g/m^3$. The prevalence of cough (measured by questionnaire) correlated significantly with pollution levels (chi-square for trend = 5.6, $p = 0.02$). No significant differences existed among the groups of subjects over 3 years, and pulmonary function and lung growth over the study were roughly equal over all groups. The results tend to suggest that intermittent high level exposure to SO_2, in the presence of moderated particulate sulfate levels, produced evidence of bronchial irritation (increased cough) but no chronic effect on lung function or lung function growth.

Jedrychowski and Krzyzanowski (1988) related SO_2 and PM levels to increased rates of chronic phlegm, cough and wheezing in females living in and near Cracow, Poland. The authors suggest that the effects may have been due to hydrogen ions, but no measurements were available.

Several authors (Lave and Seskin, 1972, 1977; Chappie and Lave, 1982; Mendelsohn and Oratt, 1979; Lipfert, 1984; Ozkaynak and Spengler, 1985; Ozkaynak and Thurston, 1987) have attempted to relate mortality rates to sulfate and other pollution measurements using ecological or macroepidemiological analyses. There are significant problems and inconsistencies in results obtained across many of these analyses, as reviewed extensively by the U.S. Environmental Protection Agency (1986, 1982). For example, Lave and

Seskin (1977) reported that mortality rates were correlated with sulfates. Lipfert (1984), reanalyzing the same data, found that it was not possible to conclude whether sulfates or total respirable particulate matter had a statistically significant effect on total mortality.

In more recent extensive analyses employing a variety of model specifications and controls for possible confounding, Ozkaynak and Spengler (1985), Ozkaynak et al. (1986), and Ozkaynak and Thurston (1987) have used more sophisticated statistical approaches in an effort to improve upon some of the previous analyses of mortality and morbidity associations with air pollution in U.S. cities. The principal findings presented by Ozkaynak and Spengler (1985) concern cross-sectional analysis of the 1980 U.S. vital statistics and available air pollution data bases for sulfates, and fine, inhalable and total suspended particles. In these analyses, using multiple regression methods, the association between various particle measures and 1980 total mortality were estimated for 98 and 38 SMSA subsets by incorporating recent information on particle size relationships and a set of socioeconomic variables to control for potential confounding. Issues of model misspecification and spatial autocorrelation of the residuals were also investigated. Results from the various regression analyses indicated the importance of considering particle size, composition, and source information in modeling of PM-related health effects. In particular, particle exposure measures related to the respirable and/or toxic fraction of the aerosols, such as FP (fine particles) and sulfates were the most consistently and significantly associated with the reported (annual) cross-sectional mortality rates. On the other hand, particle mass measures that included coarse particles (e.g., TSP and IP) were often found to be nonsignificant predictors of total mortality.

The Ozkaynak and Spengler (1985) results noted above for analysis of 1980 U.S. mortality provide an interesting overall contrast to the findings of Lipfert (1984) for 1969-70 U.S. mortality data. In particular, whereas Lipfert found TSP coefficients to be most consistently statistically significant (although varying widely depending upon model specifications, explanatory variables included, etc.), Ozkaynak and Spengler found particle mass measures including coarse particles (TSP, IP) often to be nonsignificant predictors of total mortality. Also, whereas Lipfert found the sulfate coefficients to be even more unstable than the TSP associations with mortality (and questioned the credibility of the sulfate coefficients), Ozkaynak and Spengler found that particle exposure measures related to the respirable or toxic fraction of the aerosols (e.g., FP or sulfates) to be most consistently and significantly associated with annual cross-sectional mortality rates. It might be tempting to hypothesize that changes in air quality or other factors from the earlier data sets (for 1969-70) analyzed by Lipfert (1984) to the later data (for 1980) analyzed by Ozkaynak and Spengler (1985) and Ozkaynak et al. (1986) may at least partly explain their contrasting results, but there is at present no basis by which to determine if this is the case or which set of findings may or may not most accurately characterize associations between mortality and chronic PM or SO_x exposures in the United States. Ostro (1987) also reported a stronger association between several measures of morbidity (work loss days, restricted activity days, etc.) and lagged fine particle estimates than associations with prior 2-week average TSP levels in 84 U.S. cities.

Taken as a whole, these analyses are suggestive of an association between mortality or morbidity and fine particle or sulfate fraction levels found in contemporary American urban airsheds. Much still remains to be done, however, to evaluate the relative contribution of acid aerosols formed from the fine particles or sulfates to the reported health effects.

6.3.3 Chronic Studies Relating Health Effects to Oxides of Nitrogen

Nitrates, formed from nitrogen dioxide and other oxides of nitrogen, can ultimately contribute to acid aerosol formation in ambient air under certain atmospheric conditions. Studies evaluating nitrate (as a crude surrogate for acid aerosols) effects on human health are, therefore, of some interest here.

The area surrounding the city of Chattanooga, Tennessee provided a unique opportunity to study the effects of the oxides of nitrogen without the high concentrations of other pollutants usually associated with automotive and industrial pollution. A large TNT plant, located northeast of Chattanooga, produced a substantial proportion of all trinitrotoluene (TNT) made in the United States during World War II and the Korean War. The plant was reopened in April, 1966 to supply munitions for use in Vietnam. By the this time, the area surrounding the plant had become an upper-middle-class residential neighborhood. Epidemiological studies were done in the late 1960's and early 1970's. There were, however, no measurements made of acidity and, furthermore, many of the NO_2 measurements made using the Jacobs-Hochheiser method had a number of instrumental and analytical problems. The measured levels of the oxides of nitrogen were nevertheless clearly quite high. For example, annual averages of nitrogen dioxide reached 412 $\mu g/m^3$ near the arsenal, and nitrate fraction levels reached 4.1 $\mu g/m^3$ at the downtown post office. It is likely that the elevated nitrogen dioxide levels were accompanied with elevated nitric acid levels, although no direct measurements were made. The U.S. Environmental Protection Agency (1971) measured several factors related to ambient air pollution including corrosion of zinc, steel and nylon. The corrosion levels in Chattanooga in 1967 and 1968 were among the highest, and in the case of nylon, were 10 to 100 times the levels of most other cities. According to the report, the arsenal was known to emit acid aerosols. Thus it is likely that any adverse health effects seen in Chattanooga during this time period were associated either with NO_2 itself or with the nitric acid rather than other oxides of nitrogen.

Shy et al. (1970) reported the results of a lung function study done in the same area during the 1968-1969 school year. Ventilatory lung function ($FEV_{0.75}$) was measured in elementary school children in four areas near Chattanooga. Average annual nitrogen dioxide levels ranged from 412 $\mu g/m^3$ in the high exposure area to 59 $\mu g/m^3$ in the low exposure area. Suspended nitrate levels ranged from 7.3 $\mu g/m^3$ in the high area to 1.6 $\mu g/m^3$ in the low area, but the results were not completely consistent with the gradient.

Pearlman et al. (1971) reported the results of a respiratory disease survey done in the Chattanooga area in 1969. The study reported illness rates in children for the period June, 1966 to June, 1969. Higher rates of bronchitis in school aged children were found in both the intermediate and high exposure areas as compared with the low exposure area. The results were not completely consistent with the gradient since the rate in the intermediate area was just as high as the high pollution area.

Love et al. (1982) studied acute respiratory disease in the same area during the years 1972 to 1973. Fathers, mothers, school children and preschool children all showed significantly higher rates in the area designated as high pollution area during the beginning of 1972. There were almost no significant differences in rates during the periods September to December, 1972, and January to April, 1973. During the period January to June, 1972 nitrogen dioxide levels ranged from 60.2 $\mu g/m^3$ in the high area to 28.9 $\mu g/m^3$ in the low area. However, by the second half of 1972, the exposures in all areas were quite comparable because of reduced emissions. Thus the results of the study tend to confirm the chronic effect of nitrogen dioxide or its by-products on acute respiratory disease, including quite plausibly nitric acid effects.

6.3.4 Chronic Exposure Effects in Occupational Studies

The last remaining type of information considered here concerns the effects of chronic exposures to acid aerosols in occupational settings. Such studies are discussed mainly in order to provide some perspective on the variety of health effects associated with acid aerosol exposures, even at extremely high concentrations not likely to occur in ambient air.

Gamble et al. (1984a) studied pulmonary function and respiratory symptoms in 225 workers in five lead battery acid plants. This acute effect study obtained personal samples of H_2SO_4 taken over the shift. Most personal samples were less than 1 mg/m^3 H_2SO_4. Mass median aerodynamic diameter of H_2SO_4 averaged about 5 µm. The authors concluded that exposure to sulfuric acid mist at these plants showed no significant association with symptoms or with acute effect on pulmonary function. The ability of the body to neutralized acidity of H_2SO_4 was considered as a factor is this outcome. Additionally, the authors noted that tolerance to H_2SO_4 may develop in workers habitually exposed.

In a related study of chronic effects of sulfuric acid on the respiratory system and teeth, Gamble et al. (1984b) measured in the same workers respiratory symptoms, pulmonary function, chest radiographs, and tooth erosion. Concentrations measured at the time of the study were usually 1 mg/m^3 or less. Exposure to the concentration of acid mist showed no significant association with cough, phlegm, dyspnea, wheezing, most measures of pulmonary function, and abnormal chest radiographs. Tooth etching and erosion were strongly related to acid exposure. The authors noted that the absence of a marked effect of acid exposure on respiratory symptoms and pulmonary function may be due to the size of the acid particles. The range of the mass median diameter in the 5 plants was 2.6 to 10 µm. The relative humidity of the lung would at least double particle size and many acid particles would be deposited in the upper respiratory tract. The particle size distribution of acid mist in battery plants is larger than that observed in ambient air pollutants (several micrometers in diameter compared to submicron diameters). Finally the authors note that the lack of any convincing finding in this study relating to the respiratory symptoms is not completely unexpected because of the relatively low exposure (<1 mg/m^3) compared to previous occupational studies.

Williams (1970) studied sickness absence and ventilatory capacity of workers exposed to high concentrations of sulfuric acid mist in the forming department of a battery factory (location not stated). Based on 38 observations made on two days, the forming department had a mean H_2SO_4 concentration of 1.4 mg/m^3, ranging from a trace to 6.1 mg/m^3. In a different forming department, the mass median diameter of the acid particles was 14 µm. Compared with control groups, men exposed to the high concentrations of sulfuric acid mist in the forming department had slight increases in respiratory disease, particularly bronchitis. There was no evidence of increased lower respiratory disease, which might be explained by the large particle size. After adjusting for circadian variations, there was no evidence of decreased ventilatory function.

El-Sadik et al. (1972) studied lung function, salivary pH, and dental anomalies in 33 workers in the manufacturing department of two battery factories (presumably in Egypt). Control subjects were taken from comparably aged workers in the same plants who were not exposed to chemicals. Air samples showed concentrations of sulfuric acid vapor ranging from 26 to 35 mg/m^3 in one plant, and from 12 to 14 mg/m^3 in another. Changes were found in FEV_1, dental lesions, tooth erosion, and pH of saliva, and bronchopulmonary diseases. These changes were either not statistically significant, or were not tested due to the small sample sizes. The results were suggestive, however.

6.4 SUMMARY AND CONCLUSIONS

To date, no epidemiological studies have related health effects to measured elevated ambient acid concentrations alone. The following summary contains studies where acid levels were measured and studies where the presence of acid aerosols is assumed in the ambient air mixture of pollutants but where no actual measurements were made. The results are summarized in Tables 6-1 and 6-2.

Historically important fog episodes believed to contain high levels of acids resulted in mortality and morbidity. The health effects are believed to have resulted from intense local irritant action on the lungs, which may have led to acute anoxia due to either bronchospasm or exudate in the respiratory tract. Those persons especially affected by the fogs were those suffering from asthma, chronic bronchitis and heart disease. Common symptoms were cough and dyspnea. Limited estimates or actual measurements of acid levels present

TABLE 6-1. ACUTE EXPOSURE HEALTH EFFECTS SEEN UNDER CONDITIONS OF MEASURED OR PRESUMED ACID AEROSOL EXPOSURE

Study	Exposure	Health Effects Seen
Lippmann et al. (1983) lung function study of 83 children aged 8 to 13 at a summer camp in Indiana, PA	H_2SO_4 less than 5 $\mu g/m^3$	None related to H_2SO_4
Bock et al. (1985) lung function study of 39 children at summer camp in Mendham, NJ	Low levels of H^+	None related to H^+
Lioy et al. (1985) lung function study of 91 children at a summer camp in Fairview Lake, NJ	H_2SO_4 less than 4 $\mu g/m^3$	None related to H_2SO_4
Franklin et al. (1985) lung function study of at summer camp at Lake Couchiching, Ontario, Canada	H_2SO_4 less than 5 $\mu g/m^3$	No association reported
Raizenne et al. (1988) lung function study of 112 children at Camp Kiawa, Ontario, Canada	H_2SO_4 exceeding 40 $\mu g/m^3$	FEV_1 and PEF decrements associated with air pollutant events (high acid and ozone levels)
Bates and Sizto (1983, 1986, 1987, 1988) hospital admissions study in Southern Ontario, Canada	Daily sulfate levels as high as 38 $\mu g/m^3$	Respiratory admissions (e.g., for asthma) significantly related to sulfates and ozone in the summer
Martin and Bradley (1960); Waller (1963); Commins (1963); Lawther et al. (1970); Mazumdar et al. (1982); Ostro (1984); Schwarts and Marcus (1986) analyses of London mortality and morbidity during 1950's to 1970's	Typical daily acidity concentration of 18 $\mu g/m^3$ (winter) and 7.0 $\mu g/m^3$ (summer), but very high acid droplet levels ranging up to 678 $\mu g/m^3$ during severe episodes	Bronchial irritation, dyspnea, and other symptoms. Deaths from respiratory and cardiovascular conditions
Thurston et al. (1988) reanalysis of London mortality data for 1963-1972 winters	Daily direct acid aerosol measurements with maximum 24-hr levels ranging up to 40-134 $\mu g/m^3$ (as H_2SO_4 equivalent)	Stronger correlation of acid aerosols with unadjusted total mortality than for BS or SO_2, but association remains to be confirmed by more sophisticated time-series analysis

TABLE 6-2. CHRONIC EXPOSURE HEALTH EFFECTS SEEN UNDER CONDITIONS OF MEASURED OR PRESUMED ACID AEROSOL EXPOSURE

Study	Exposure	Health Effects Seen
Kitagawa (1984) study of asthma episodes in Yokkaichi, Japan from 1960 to 1969	High SO_3/SO_2 ratios. Presumed high levels of H_2SO_4	Increased asthma episodes
Franklin et al. (1985) chronic cross-sectional study of 1,141 children in Canada	Sulfate, SO_2, NO_2, PM_{10}, and NO_3	Two percent decrease in FVC
Ware et al. (1986) six city Harvard study of children in the eastern and midwestern U.S.	Annual sulfate levels ranged from 4.5 to 19.3 $\mu g/m^3$	Chronic cough was related to sulfates, but lung function was not
Speizer (1988) bronchitis prevalence rates in 4 of Harvard's six city study	H^+, PM_{15}	Better correlation of bronchitis prevalence with H^+ than with PM_{15}
Chapman et al. (1985) four city study of chronic disease in young adults in Utah	Annual sulfate levels ranged from 5 to 14 $\mu g/m^3$	Persistent cough and phlegm were related to SO_2 and sulfate levels
Schenker et al. (1983) study of respiratory disease in women in rural Pennsylvania	Four year average SO_2 levels ranged from 62 to 99 $\mu g/m^3$	Wheeze was associated with increased SO_2, but cough and phlegm were not
Dodge et al. (1985) longitudinal study of children in southeastern U.S. towns	Peak 3 hour SO_2 exceeded 2,500 $\mu g/m^3$. Sulfates also present	Prevalence of cough was related to intermittent high SO_2 in the presence of sulfates
Shy et al. (1970) study of lung function in children in Chattanooga	Annual NO_2 levels ranged from 59 to 412 $\mu g/m^3$, nitrate levels from 1.6 to 7.3 $\mu g/m^3$, probably HNO_3	Inconsistent decreased pulmonary function related to both pollutants
Pearlman et al. (1971) study of respiratory disease rates in children in Chattanooga	Annual NO_2 59 to 412 $\mu g/m^3$, nitrate 1.6 to 7.2 $\mu g/m^3$, probably HNO_3	Inconsistent increased bronchitis rates

during London episodes, provide some indications of likely involvement of ambient acid aerosols in producing reported health effects.

United States and Canadian acute summer camp studies measured H^+ concentrations, all but the Razienne et al. (1988) study, had acid (H_2SO_4) concentrations less than 5 μg/m^3. No changes in pulmonary function could be found related to these lower levels. The one study with acid (H_2SO_4) levels above 40 μg/m^3 did not separate the effects of acids from copollutants such as ozone (Raizenne et al., 1988). Further analysis may do this. Bates and Sizto (1983, 1986, 1987, 1988) related hospital admissions for respiratory diseases (including asthma) to sulfate and ozone levels in the summer in Canada and speculate that acid aerosols may be more directly related.

Several researchers examined the European acid event of 1985 which extended from western Germany to Great Britain. However, no studies had adequate acid aerosol data by which to attempt detailed analyses that might demonstrate direct health effects relationships to acid levels.

Among the chronic studies, Kitagawa (1984) attempted to measure acidity in the air of one city of Japan where chronic health effects episodes occurred. The study found increased bronchitis, pulmonary emphysema, and mortality from asthma and chronic bronchitis. Actual acid mist levels are difficult to estimate from this study.

Franklin et al. (1985) and Raizenne et al. (1987b) report pulmonary function decrements for a pollution mix in Canada but not for acid aerosols or sulfates alone. The Ware et al. (1986) study suggests that sulfate levels are related to bronchitis and some other respiratory disorders in young children, but sulfate levels are not related to pulmonary function measures. Speizer (1988) notes that, in four cities of the Harvard six city study where acid levels were determined, there was a better correlation of bronchitis prevalence with H^+ than with PM_{15}. The Chapman et al. (1985) study suggests that SO_2 and sulfate levels are related to persistent cough and phlegm in young parents. Dodge et al. (1985) found that prevalence of cough in children correlated with SO_2 and sulfate levels. Ozkaynak and Spengler (1985) also found that mortality is also more strongly related to fine particles and sulfate levels than to total suspended particulate levels. Consistent with this are Ostro's (1988) reported similar stronger associations between morbidity indicators and estimated fine particle levels versus TSP levels.

Elevated levels of oxides of nitrogen may also have been correlated with elevated acid levels in Chattanooga, TN. Pearlman et al. (1971) found some suggestion of increased bronchitis rates in school aged children associated with NO_2 and nitrate fraction levels. Love et al. (1982) found that fathers, mothers, school children, and preschool children all showed significantly higher rates of acute respiratory disease in the areas with higher pollution levels. Shy et al. (1970) found slightly decreased lung function in school aged children in the areas of higher pollution, although the results were not completely consistent.

Lioy and Lippman (1986) comment that situations exist where atmospheric H_2SO_4 at current North American exposure levels may be the active agent in causing respiratory responses. There are at least two scales on which this may occur: (1) locally, downwind of a plume, and (2) regionally, downwind of major source areas. The highest acid concentrations observed appear to be associated with direct plume impacts. Therefore, these locations warrant considerable attention in future epidemiological studies.

From among the occupational studies, the Williams (1970) results are most notable. This study found that men exposed to H_2SO_4 levels of 1.4 to 6.1 mg/m^3 had increases in respiratory disease, particularly bronchitis.

When taken as a whole, the epidemiological studies can provide indications that ambient acid aerosols have likely been associated with certain types of observed health effects in some situations and the available results help to highlight directions for future research. It appears that respiratory disease effects such as asthma, persistent cough and phlegm, and bronchitis are easier to detect than are decreases in pulmonary function. This is consistent with the results of the human clinical studies reported in Chapter 5. Also, alterations in mucociliary transport rates could be seen with repeated exposures of 100 $\mu g/m^3$ in animal toxicological studies as discussed in Chapter 4, which may be related to the development of chronic obstructive pulmonary disease (Lippmann et al., 1987). Lippmann et al. (1982) have also shown that the effects of H_2SO_4 and cigarette smoke are essentially the same on bronchial mucociliary clearance patterns.

The one clear conclusion that can be reached from these studies is that there is a compelling need for additional research. Although there are a few new studies that may be published in the near future, it is likely that the results of these studies will be inconclusive due to the sparsity of actual measurements of ambient acidity levels. New studies using improved acid measurement technology and measuring some of the health endpoints described earlier are critical in order to provide more definitive evaluations of health effects associated with ambient acids. As one example, Speizer (1988) has reported on a new large scale study just begun which would directly assess the chronic effects of acid aerosols on the respiratory health of children. That multi-city study is to be done collaboratively by Harvard University and Health and Welfare, Canada. The study will have three sets of eight sites, with approximately 700 children being examined at each site. Sites will be chosen to represent gradients in ozone, hydrogen ions from sulfur oxides, and hydrogen ions from nitrogen oxides. Hopefully, such measurements of acid aerosol parameters will allow for critically needed direct evaluations of acid aerosol effects on human health under ambient conditions.

6.5 REFERENCES

Annesi, I.; Kauffmann, F. (1986) Is respiratory mucus hypersecretion really an innocent disorder? A 22-year mortality survey of 1,061 working men. Am. Rev. Respir. Dis. 134: 688-693.

Ayres, J.; Fleming, D.; Williams, M.; McInnes, G. (1988) Measurement of respiratory morbidity in general practice in the UK during the acid transport event of January 1985. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Bates, D. V. (1983) Ecclesiastes reread. Am. Rev. Respir. Dis. 128: 383-384.

Bates, D. V.; Sizto, R. (1983) Relationship between air pollutant levels and hospital admissions in Southern Ontario. Can. J. Pub. Health 74: 117-122.

Bates, D. V.; Sizto, R. (1986) A study of hospital admissions and air pollutants in southern Ontario. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment and control strategies: proceedings of the 2nd US-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 767-777.

Bates, D. V.; Sizto, R. (1987) Air pollution and hospital admissions in Southern Ontario: the acid summer haze effect. Environ. Res. 43: 317-331.

Bates, D. V.; Sizto, R. (1988) The Ontario air pollution study: identification of the causative agent. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Bock, N.; Lippmann, M.; Lioy, P.; Munoz, A.; Speizer, F. E. (1985) The effects of ozone on the pulmonary function of children. In: Lee, S. D. Evaluation of the scientific basis for ozone/oxidants standards: proceedings of an APCA international specialty conference; November 1984; Houston, TX. Pittsburgh, PA: Air Pollution Control Association; pp. 297-308.

Chapman, R. S.; Calafiore, D. C.; Hasselblad, V. (1985) Prevalence of persistent cough and phlegm in young adults in relation to long-term ambient sulfur oxide exposure. Am. Rev. Respir. Dis. 132: 261-267.

Chappie, M.; Lave, L. (1982) The health effects of air pollution: a reanalysis. J. Urban Econ. 12: 346-376.

Commins, B. T. (1963) Determination of particulate acid in town air. Analyst (London) 88: 364-367.

Dassen, W.; Brunekreef, B.; Hoek, G.; Hofschreuder, P.; Staatsen, B.; de Groot, H.; Schouten, E.; Biersteker, K. (1986) Decline in children's pulmonary function during an air pollution episode. J. Air Pollut. Control Assoc. 36: 1223-1227.

de Leeuw, F. A. A. M.; van Rheineck Leyssius, H. J. (1988) Long-range transport modelling of air pollution episodes. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Dockery, D. W.; Ware, J. H.; Ferris, B. G., Jr.; Speizer, F. E.; Cook, N. R.; Herman, S. M. (1982) Change in pulmonary function in children associated with air pollution episodes. J. Air Pollut. Control Assoc. 32: 937-942.

Dodge, R.; Solomon, P.; Moyers, J.; Hayes, C. (1985) A longitudinal study; of children exposed to sulfur oxides. Am. J. Epidemiol. 121: 720-736.

El-Sadik, Y. M.; Osman, H. A.; El-Gazzar, R. M. (1972) Exposure to sulfuric acid in manufacture of storage batteries. JOM J. Occup. Med. 14: 224-226.

Ferris, B. G., Jr.; Ware, J. H.; Spengler, J. D.; Dockery, D. W.; Speizer, F. E. (1986) The Harvard six-cities study. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment and control strategies: proceedings of the second U. S.-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 721-730.

Firket, M. (1931) The causes of accidents which occurred in the Meuse Valley during the fogs of December 1930. Bull. Acad. R. Med. Belg. 11[ser. 5]: 683-741.

Franklin, C. A.; Burnett, R. T.; Paolini, R. J. P.; Raizenne, M. E. (1985) Health risks from acid rain: a Canadian perspective. EHP Environ. Health Perspect. 63: 155-168.

Gamble, J.; Jones, W.; Hancock, J. (1984a) Epidemiological-environmental study of lead acid battery workers. II. Acute effects of sulfuric acid on the respiratory system. Environ. Res. 35: 11-29.

Gamble, J.; Jones, W.; Hancock, J.; Meckstroth, R. L. (1984b) Epidemiological-environmental study of lead acid battery workers. III. Chronic effects of sulfuric acid on the respiratory system and teeth. Environ. Res. 35: 30-52.

Hemeon, W. C. L. (1955) The estimation of health hazards from air pollution. Arch. Ind. Health 11: 397-402.

Jedrychowski, W.; Krzyzanowski, M. (1988) Ventilatory lung function and chronic chest symptoms among the inhabitants of urban areas with various levels of acid aerosols. The prospective study in Cracow. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Kitagawa, T. (1984) Cause analysis of the Yokkaichi asthma episode in Japan. J. Air Pollut. Control Assoc. 34: 743-746.

Koenig, J. Q.; Pierson, W. E.; Horike, M. (1983) The effects of inhaled sulfuric acid on pulmonary function in adolescent asthmatics. Am. Rev. Respir. Dis. 128: 221-225.

Lave, L. B.; Seskin, E. P. (1972) Air pollution, climate, and home heating: their effects on U.S. mortality rates. Am. J. Public Health 62: 909-916.

Lave, L. B.; Seskin, E. P. (1977) Air pollution and human health. Baltimore, MD: The Johns Hopkins University Press.

Lawther, P. J.; Waller, R. E.; Henderson, M. (1970) Air pollution and exacerbations of bronchitis. Thorax 25: 525-539.

Lioy, P. J.; Lippmann, M. (1986) Measurement of exposure to acidic sulfur aerosols. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment and control strategies: proceedings of the second U. S.-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 743-752.

Lioy, P. J.; Vollmuth, T. A.; Lippmann, M. (1985) Persistence of peak flow decrement in children following ozone exposures exceeding the national ambient air quality standard. J. Air Pollut. Control Assoc. 35: 1068-1071.

Lioy, P. J.; Spektor, D.; Thurston, G.; Citak, K.; Lippmann, M.; Bock, N.; Speizer, F. E.; Hayes, C. (1987) The design considerations for ozone and acid aerosol exposure and health investigations: the Fairview Lake summer camp-photochemical smog case study. Environ. Int. 13: 271-283.

Lipfert, F. W. (1984) Air pollution and mortality=specification searches using SMSA-based data. J. Environ. Econ. Manage. 11: 208-243.

Lippmann, M.; Gearhart, J. M.; Schlesinger, R. B. (1987) Basis for a particle size-selective TLV for sulfuric acid aerosols. Appl. Ind. Hyg. 2: 188-199.

Lippmann, M. (1985) Airborne acidity: estimates of exposure and human health effects. EHP Environ. Health Perspect. 63: 63-70.

Lippmann, M.; Schlesinger, R. B.; Leikauf, G.; Spektor, D.; Albert, R. E. (1982) Effects of sulphuric acid aerosols on respiratory tract airways. In: Walton, W. H., ed. Inhaled particles V: proceedings of an international symposium organized by the British Occupational Hygiene Association; September 1980; Cardiff, United Kingdom; Ann. Occup. Hyg. 26: 677-690.

Lippmann, M.; Lioy, P. J.; Leikauf, G.; Green, K. B.; Baxter, D.; Morandi, M.; Pasternack, B. S.; Fife, D.; Speizer, F. E. (1983) Effects of ozone on the pulmonary function of children. In: Lee, S. D.; Mustafa, M. G.; Mehlman, M. A., eds. International symposium on the biomedical effects of ozone and related photochemical oxidants; March 1982; Pinehurst, NC. Princeton, NJ: Princeton Scientific Publishers, Inc.; pp. 423-446. (Advances in modern toxicology: v. 5).

Love, G. J.; Lan, S.-P.; Shy, C. M.; Riggan, W. B. (1982) Acute respiratory illness in families exposed to nitrogen dioxide ambient air pollution in Chattanooga, Tennessee. Arch. Environ. Health 37: 75-80.

Martin, A. E. (1964) Mortality and morbidity statistics and air pollution. Proc. R. Soc. Med. 57: 969-975.

Martin, A. E.; Bradley, W. H. (1960) Mortality, fog and atmospheric pollution:; an investigation during the winter of 1958-59. Mon. Bull. Minist. Health Public Health Lab. Serv. G. B. 19: 56-73.

Mazumdar, S.; Schimmel, H.; Higgins, I. T. T. (1982) Relation of daily mortality to air pollution: an analysis of 14 London winters, 1958/59-1971/72. Arch. Environ. Health 37: 213-220.

Mendelsohn, R.; Orcutt, G. (1979) An empirical analysis of air pollution dose-response curves. J. Environ. Econ. Manage. 6: 85-106.

Ostro, B. (1984) A search for a threshold in the relationship of air pollution to mortality: a reanalysis of data on London winters. EHP Environ. Health Perspect. 58: 397-399.

Ostro, B. D. (1987) Air pollution and morbidity revisited: a specification test. J. Environ. Econ. Manage.: in press.

Ozkaynak, H.; Spengler, J. D. (1985) Analysis of health effects resulting from population exposures to acid precipitation precursors. In: Conference on health effects of acid precipitation; November 1984; Research Triangle Park, NC. EHP Environ. Health Perspect. 63: 45-55.

Ozkaynak, H.; Thurston, G. D. (1987) Associations between 1980 U.S. mortality rates and alternative measures of airborne particle concentration. Risk Anal. 7: 449-461.

Ozkaynak, H.; Spengler, J. D.; Garsd, A.; Thurston, G. D. (1986) Assessment of population health risks resulting from exposures to airborne particles. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment and control strategies, proceedings of the second U.S.-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 1067-1080.

Pearlman, M. E.; Finklea, J. F.; Creason, J. P.; Shy, C. M.; Young, M. M.; Horton, R. J. M. (1971) Nitrogen dioxide and lower respiratory illness. Pediatrics 47: 391-398.

Peto, R.; Speizer, F. E.; Cochrane, A. L.; Moore, F.; Fletcher, C. M.; Tinker, C. M.; Higgins, I. T. T.; Gray, R. G.; Richards, S. M.; Gilliland, J.; Norman-Smith, B. (1983) The relevance in adults of air-flow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease: results from 20 years of prospective observation. Am. Rev. Respir. Dis. 128: 491-500.

Raizenne, M.; Spengler, J.; Oskaynak, H.; Burnett, R. (1986) Short-term respiratory health effects of transported air pollutants in children. Am. Rev. Respir. Dis. 132: A217.

Raizenne, M. E.; Hargreave, F.; Sears, M.; Spengler, J.; Stern, B.; Burnett, R. (1987a) Exercise and lung function responses during an air pollution episode in young females with airway hyperresponsiveness to methacholine. Am. Rev. Respir. Dis. 135: A343.

Raizenne, M.; Burnett, R.; Stern, B.; Meranger, J. C. (1987b) Transported air pollutants and respiratory health in two Canadian communities. Chest 91: 314.

Raizenne, M. E.; Stern, B.; Burnett, R.; Franklin, C. A.; Spengler, J. D. (1988) Acute lung function responses to ambient acid aerosol exposures in children. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Schenker, M. B.; Samet, J. M.; Speizer, F. E.; Gruhl, J.; Batterman, S. (1983) Health effects of air pollution due to coal combustion in the Chestnut Ridge region of Pennsylvania: results of cross-sectional analysis in adults. Arch. Environ. Health 38: 325-330.

Schrenk, H. H.; Heimann, H.; Clayton, G. D.; Gafafer, W. M.; Wexler, H. (1949) Air pollution in Donora, Pa.: epidemiology of the unusual smog episode of October 1948, preliminary report. Washington, DC: Federal Security Agency, Public Health Service; Public Health Bulletin no. 306.

Schwartz, J.; Marcus, A. H. (1986) Statistical reanalyses of data relating mortality to air pollution during London winters 1958-1972. Washington, DC: U. S. Environmental Protection Agency, Office of Policy, Planning and Evaluation.

Shy, C. M.; Creason, J. P.; Pearlman, M. E.; McClain, K. E.; Benson, F. B.; Young, M. M. (1970) The Chattanooga school children study: effects of community exposure to nitrogen dioxide. 1. Methods, description of pollutant exposure, and results of ventilatory function testing. J. Air Pollut. Control Assoc. 20: 539-545.

Speizer, F. E. (1988) Studies of acid aerosols in six cities and in a new multicity investigation: design issues. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Spektor, D. M.; Lippmann, M.; Lioy, P. J.; Thurston, G. D.; Citak, K.; Bock, N.; Speizer, F. E.; Hayes, C. (1988a) Effects of ambient ozone on respiratory function in active normal children. Am. Rev. Respir. Dis.: in press.

Spektor, D. M.; Yen, B. M.; Lippman, M. (1988b) Effect of concentration and cumulative exposure of inhaled sulfuric acid on tracheobronchial particle clearance in healthy humans. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Spengler, J. D.; Allen, G. A.; Foster, S.; Severance, P.; Ferris, B., Jr. (1986) Sulfuric acid and sulfate aerosol events in two U.S. cities. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P., eds. Aerosols: research, risk assessment and control strategies: proceedings of the 2nd U. S.-Dutch internationalsymposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 107-120.

Spengler, J. D.; Keeler, G. J.; Koutrakis, P.; Raizenne, M. (1988) Exposure to acidic aerosols. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Thurston, G. D.; Ito, K.; Lippmann, M.; Hayes, C. (1988) Re-examination of London, England mortality in relation to exposure to acidic aerosols during 1963-1972 winters. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

U. S. Environmental Protection Agency. (1971) Interstate surveillance project: measurement of air pollution using static monitors. Research Triangle Park, NC: Air Pollution Control Office.

U. S. Environmental Protection Agency. (1982) Air quality criteria for particulate matter and sulfur oxides. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report nos. EPA-600/8-82-029aF-cF. 3v. Available from: NTIS, Springfield, VA; PB84-156777.

U. S. Environmental Protection Agency. (1986) Second addendum to air quality criteria for particulate matter and sulfur oxides (1982): assessment of newly available health effects information. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA/600/8-86/020F.

United Kingdom Ministry of Health. (1954) Mortality and morbidity during the London fog of December 1952. London, United Kingdom: Her Majesty's Stationary Office. (Reports on public health and medical subjects no. 95).

Utell, M. J.; Morrow, P. E.; Speers, D. M.; Darling, J.; Hyde, R. W. (1983) Airway responses to sulfate and sulfuric acid aerosols in asthmatics: an exposure-response relationship. Am. Rev. Respir. Dis. 128: 444-450.

Waller, R. E. (1963) Acid droplets in town air. Int. J. Air Water Pollut. 7: 773-778.

Waller, R. E.; Lawther, P. J. (1957) Further observations on London fog. Br. Med. J. 4: 1473-1475.

Ware, J. H.; Ferris, B. G., Jr.; Dockery, D. W.; Spengler, J. D.; Stram, D. O.; Speizer, F. E. (1986) Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. Am. Rev. Respir. Dis. 133: 834-842.

Wichmann, H. E.; Mueller, W.; Allhoff, P.; Beckmann, M.; Bocter, N.; Csicsaky, M. J.; Jung, M.; Molik, B.; Schoenberg, G. (1988) Health effects during a smog-episode in West Germany in 1985. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Williams, M. K. (1970) Sickness absence and ventilatory capacity of workers exposed to sulphuric acid mist. Br. J. Ind. Med. 27: 61-66.

7. CONSIDERATIONS FOR LISTING ACID AEROSOLS AS A CRITERIA POLLUTANT

7.1 INTRODUCTION

7.1.1 Purpose

This chapter assesses and integrates the most relevant scientific and technical discussion in the preceding chapters that the EPA staff believes should be considered for the possible listing of acid aerosols as a criteria air pollutant. This assessment is intended to help bridge the gap between the scientific review and the judgments required of the Administrator in a listing decision. As such, particular emphasis is placed on identifying those conclusions and uncertainties in the available scientific literature that the staff believes should be considered in a possible listing decision.

Because this document is concerned only with the health risks of acid aerosols, a discussion of the potential welfare effects of acid aerosols is beyond the scope of this chapter.

7.1.2 Background

Section 108 of the Clean Air Act provides for the listing of certain ubiquitous ambient air pollutants that are reasonably anticipated to endanger public health. Once an air pollutant is listed, Sections 108-109 of the Act require issuance of air quality criteria and proposal of national ambient air quality standards (NAAQS) for the pollutant within 12 months. Section 110 then requires the development of State implementation plans (SIPs) to implement the standards.

In response to these requirements, EPA has listed a number of air pollutants under Section 108, including particulate matter, sulfur oxides, and nitrogen oxides; issued the requisite air quality criteria and NAAQS for these pollutants; and approved or promulgated SIPs to implement the NAAQS. As a result, acid aerosols and their principal precursors are currently regulated to varying degrees by these existing national ambient air quality standards. In general, the existing standards are met throughout most of the U.S., and levels of these pollutants in the ambient air have generally been stable or declining in recent years. Major increases in emissions of such pollutants are not anticipated in most areas of the country.

7.1.3 Approach

The approach used in this chapter is to assess and integrate information derived from the preceding chapters in order to address the central question of whether the available information provides sufficient and compelling evidence to proceed with the separate listing of acid aerosols. Particular attention is drawn to those critical elements that the staff believes should be considered in a decision whether to proceed with a separate listing of acid aerosols and to those judgments that must be based on the careful interpretation of incomplete or uncertain evidence.

Section 7.2 examines the major considerations for listing acid aerosols. Section 7.2.1 discusses available data for characterizing and defining acid aerosols. This section also examines possible exposure scenarios to support discussions of the available health effects studies. Section 7.2.2 presents information on health effects of concern and of sensitive population groups, and summarizes the most relevant animal, controlled human, and epidemiological studies. Section 7.2.3 reviews the sources of acid aerosols and their precursors. Section 7.2.4 examines briefly the implications of listing acid aerosols for the ambient standards program.

The final section of the chapter (7.3) presents alternative courses of action regarding a listing decision in light of the available scientific information.

7.2 CONSIDERATIONS FOR LISTING ACID AEROSOLS UNDER SECTION 108 OF THE CLEAN AIR ACT

7.2.1 Characterization of Acid Aerosols

Acid aerosols can be defined and measured in several ways. Chapter 2 discusses the available information to characterize atmospheric acids as well as available monitoring techniques. Acid sulfates are the major species in ambient acid aerosols; at times, sulfuric acid (H_2SO_4) and ammonium bisulfate (NH_4HSO_4) may account for all of the aerosol strong acidity (Morandi et al., 1983). Other species, particularly nitric acid (HNO_3), may be of importance in certain exposure situations, such as acid fogs in western coastal cities. Under typical ambient conditions, nitric acid is usually a vapor.

A number of different "indicators," defined by the measurement method employed, have been used to characterize acid aerosols in the ambient air. As discussed in Chapter 2, measurement methodologies have various degrees of species resolution, time resolution, recovery abilities, neutralization control, and sampling anomalies. Table 7-1 presents various indicators with comments regarding the merits of each to characterize human exposures.

A key consideration in a decision to list acid aerosols is whether any one of these measures is sufficient and appropriate to define acid aerosols clearly, and thus serve as the pollutant indicator for regulatory purposes. A standardized measurement method is essential, but to date no organized program exists to develop recommended techniques or to systematically evaluate the relative uncertainties of the available methods and data from individual studies. In addition, it is not clear that the health effects data are sufficiently developed at this time to identify an indicator that best encompasses ambient exposures of concern.

Ambient monitoring data available to characterize spatial and temporal relationships of acid aerosols are sparse and interpretation must be tempered by the limitations of the diverse methodologies employed. Chapter 2 reviews the available studies. Although limited, this information does yield the following general conclusions regarding ambient levels of acid aerosols and their spatial and temporal relationships.

1) A wide range of acid levels (H_2SO_4 or H^+ as H_2SO_4) and acid "events" have been observed in contemporary North American atmospheres (see Tables 2-8 to 2-15). Concentrations of H_2SO_4 from zero to nearly 50 $\mu g/m^3$, 1 h maximum (Spengler et al., 1988), have been measured, with most levels <5 $\mu g/m^3$. In studies where only H_2SO_4 was measured, total aerosol strong acidity is probably underestimated; at times the majority of strong acid appears to be associated with partially neutralized ammonium salts (i.e., NH_4HSO_4) rather than H_2SO_4 (Morandi et al., 1983; Thurston and Waldman, 1987).

2) Ammonia neutralization plays a key role in determining the persistence of atmospheric acids (see Section 2.2.5). Additionally, ammonia sources may locally modify acid levels of regional events (Thurston and Waldman, 1987).

TABLE 7-1. ALTERNATIVE INDICATORS FOR CHARACTERIZING EXPOSURE TO ACID AEROSOLS

Indicator	Comments
Individual species e.g., H_2SO_4, NH_4HSO_4, HNO_3	-H_2SO_4 directly relatable to many of the existing health studies, other species less so at this time
	-individual species may be the active component over a more generic measure, such as strong acid. On the other hand individual species may not adequately reflect the major ambient exposures of concern; species such as H_2SO_4 may not be common constituents of aerosols, yet acidity may still be high at times (e.g., high NH_4HSO_4 component)
	-need to choose one as appropriate to establish standards, or set separate standards for each
Strong acid sulfates (i.e., H_2SO_4 + NH_4HSO_4)	-probably includes the major components of most acid aerosol events
	-most studied species
	-may not adequately reflect the complete range of possible acid exposure, for example, strong acid gases such as HNO_3
	-cannot directly measure NH_4HSO_4 at this time
Strong acid	-includes all species which readily contribute to free H^+ in aerosols
	-health effects data suggest that H^+ of strong acids is the most important active species
	-does not distinguish possible importance of specific strong acids
	-possibly need to measure strong acid particles and gases
	-does not encompass total titratable H^+ i.e., weak acids
Total titratable acidity	-inclusive, all species that contribute to available H^+ are measured
	-blurs the distinction between strong and weak acids, and individual species
	-not clear that weak acids are of health concern or are important constituents in ambient aerosols
Sulfates	-large ambient data set available
	-relatable to existing epidemiological studies
	-includes major acid sulfate species
	-does not consistently relate to aerosol acidity
	-includes the nearly neutral ammonium sulfate, which at times may dominate sulfate mass
	-excludes other acidic species, e.g., HNO_3

3) Levels of sulfates and H^+ appear to be highest in the summer (Ferek et al., 1983; Spengler et al., 1988). Large areas of the Northeast, extending into Canada, may be affected by elevated acid concentrations over extended periods at this time (Pierson et al., 1980; Lioy et al., 1980; Stevens et al., 1978; Thurston and Waldman, 1987).

4) Urban areas may be a significant source of ammonia and there is evidence that acid levels are lower in urban areas than in rural or upwind areas, particularly during regional events (Tanner et al., 1981; Thurston and Waldman, 1987, see also Section 2.7.1 and Table 2-8). However, elevated acid levels and acid events do occur in urban areas.

5) Acid levels will often show a pronounced diurnal cycle, with peak levels during daytime (cf. Stevens et al., 1980; Cobourn and Husar, 1982; Spengler et al., 1986). Ozone often has a similar pattern and hence elevated levels of ozone and acid may occur together, particularly in the summer.

6) Sulfate events may show fairly rapid swings in acidity, varying from mostly strong acid (H_2SO_4) to mostly weakly acidic ammonium salts ($(NH_4)_2SO_4$), over periods of hours to days; weak and strong acid species, however, can occur simultaneously (see Section 2.7.1).

7) With the exception of measurements made in California, nitric acid concentrations are typically less than 10 $\mu g/m^3$ (see Section 2.7.3). There are very few ambient data for HNO_3 therefore it is difficult to compare the contribution of H^+ exposures from nitric acid with acid sulfates.

8) Nitric acid vapor can be neutralized by NH_3, which coalesces into particulate NH_4NO_3. The presence of HNO_3 therefore may scavenge available ammonia, either ambient or respiratory NH_3, and influence acidity of sulfate aerosols.

9) Acid fogs, discussed in Section 2.2.4, are a special type of atmospheric aerosol. Fog droplets are very effective at scavenging pollutant materials from the air and can be highly concentrated with a variety of chemical components including acids (see Table 2-4).

Based on the available data characterizing ambient acid aerosols, the primary human exposures of interest are: large scale regional episodes, local plume impacts, and acid fogs.

Regional episodes, manifested by high H_2SO_4 and/or NH_4HSO_4 occurring over periods of one hour or more throughout a day or sequence of days, could potentially involve very large numbers of people. Moreover, elevated ozone could frequently be associated with these events. Since these episodes occur in the summer when large segments of the population, children in particular, will be participating in outdoor activities, elevated ventilation rates due to exercise and prolonged exposures may be key variables to consider in assessing health risk. Additionally, the penetration of acid aerosols indoors is estimated to be high at this time of year (Spengler et al., 1988).

The second type of exposures are confined to areas downwind of strong sources such as power plants, smelters, or combined sources in urban areas. Exposures can occur throughout the year, although most significantly in summer. Plume impacts may be different from regional sulfate episodes in having higher SO_2 and NO_x levels, high particle levels, primary acid sulfates dominated by H_2SO_4 (i.e., recently formed and little neutralized), and possibly other acids, such as HCl as well.

Acid fogs will be associated with cool temperatures and diverse chemical composition, which may be modifying factors for possible health effects of such fogs. Nitric acid is effectively scavenged to droplets in fogs (see Section 2.2.4), and thus may significantly affect acidity.

Limited data are available to characterize particle size of typical ambient acid aerosols, yet it is clear that most mass is in the fine particle fraction (<2.5 μm) and, in fact, most studies have shown mean or median mass in the submicrometer range (see Section 2.2.2). Regional acid events and plumes are probably dominated by these fine particles, whereas a key feature of acid fogs is the relatively large particle size (most mass between 5-30 μm, see Section 2.2.4). Particle size has a significant influence on regional deposition in the respiratory tract and possible health effects (see Chapter 3).

Animal studies (Chapter 4) and controlled human studies (Chapter 5) indicate that health effects may result from acute, subchronic (or repeated peak), or chronic exposures. Similarly, epidemiological studies (Chapter 6) are suggestive that acute or chronic exposures are associated with health effects. However, ambient data are insufficient at this time to assess adequately the frequency, magnitude, and duration of acid aerosol events; moreover the limited health effects data base makes interpretation of available ambient data difficult. There is a great need for focused research to quantify ambient exposures, including data on acid sulfates, nitric acid and ammonia.

In summary, the level of knowledge to characterize ambient acid aerosols is limited. There has been, as yet, no precise definition of acid aerosols, rather they are a class of pollutants that may be considered to be a subset of pollutants already regulated by existing NAAQS. Acid sulfates appear to be the major species of concern, but other acids, both particles and vapors, may be important in certain situations. There are several possible measurement techniques, but there is no accepted "standard" method, which further complicates interpreting the meager quantitative data. It is difficult, therefore, to assess exposures accurately given these limitations. Nevertheless, there is the potential for large segments of the population to be exposed to elevated acid levels, at times in combination with high levels of other pollutants such as ozone. The significance of ambient exposures in terms of health effects, however, is unclear, as will be discussed next.

7.2.2 Available Health Effects Data on Acid Aerosols

To make the decision to list acid aerosols under Section 108 of the Act, the Administrator must conclude that current ambient levels of acid aerosols may reasonably be anticipated to endanger public health. Such a judgment requires a sufficient body of supporting evidence that includes data on health effects of concern, sensitive populations, and concentration-response information from appropriate studies to measure against expected ambient exposures.

The bulk of the quantitative health effects data base for acid aerosols involves acid sulfates, primarily submicrometer H_2SO_4. There are no animal data, and limited controlled human data, for larger droplets that would be typical of acid fogs. Few data are available for nonsulfur constituents of acid fogs or other acidic atmospheres, such as nitric acid. It is essential to have a clear idea of which acid species are toxicologically important to direct efforts aimed at quantifying ambient exposures and before possible regulatory action is taken. As indicated in Chapters 4 and 5, it appears that toxicological potency is related to the strength of the acid, i.e., $H_2SO_4 > NH_4HSO_4 > (NH_4)_2SO_4$. However, Amdur et al. (1978b) found that $(NH_4)_2SO_4$ had a greater effect than NH_4HSO_4 on respiratory function in guinea pigs, whereas Schlesinger (1988) provides evidence that the H^+ associated with H_2SO_4 may be more "potent" for altering respiratory region clearance than that associated with NH_4HSO_4. There is a need to explore concentration-response relationships further in controlled studies, for example by examining different acid species and mixtures with the same pH or the same titratable acidity.

The use of distinct acid species (singly or in mixtures of pollutants) under well defined exposure conditions (i.e., concentration, particle size, time and route of exposure) are strengths of the controlled laboratory studies. At present, these studies provide the best quantitative exposure-response data and information on possible health effects of acid aerosols.

Animal studies in particular are valuable to provide data on the full range of possible effects, and are especially valuable for the study of chronic effects, providing information generally unavailable from epidemiological or controlled human studies. However, quantitative extrapolation to humans is a major limitation of animal studies; with acid aerosols some unique problems exist. Initial particle size, hygroscopic growth, ammonia neutralization, airway buffering capacity, and regional deposition, in addition to species sensitivity, may influence dose-response relationships and hence extrapolation of the data. As discussed in Chapter 4, neutralization by both endogenous and exogenous ammonia in particular may be a key variable in animal studies and may explain some of the wide variation in response among the available studies.

Controlled human studies, in addition to the advantages of controlled exposure conditions, avoid extrapolation problems of animal studies, yet they are limited inasmuch as they may not characterize the most sensitive populations (e.g., elderly, most reactive asthmatics, individuals with preexisting respiratory disease). Moreover, these studies generally examine specific, predetermined endpoints (for acid aerosols these have included respiratory function and symptoms, blood biochemistry, mucociliary clearance, and airway reactivity--See Chapter 5) and do not "search" for effects or address chronic exposures.

Lastly, controlled animal or human studies focus on single pollutants or a limited mixture of pollutants, whereas typical ambient exposures often involve a complex and changing mixture of pollutants.

In any case, the available animal and controlled human studies, while providing convincing evidence that at high enough concentrations health effects will occur, have not demonstrated effects of acid aerosols alone at concentrations in the range of known ambient conditions. However, epidemiology provides suggestive evidence that current ambient levels of acid aerosols are associated with health effects.

Some of the most interesting epidemiological studies show health effects associations with plausible surrogate acid indices (e.g., sulfates, particles) in contemporary North American environments and in areas where elevated acid levels have been found in subsequent monitoring efforts (e.g., Bates and Sitzo (1987) report the presence of elevated H^+ in the region while Speizer (1988) indicates that the prevalence of bronchitis in the 6-city study suggests a better correlation with subsequently measured H^+ data than PM_{15} data). It has been speculated that H+ may be a more likely causal agent, traveling with the measured surrogate pollutants, to explain the effects seen in some of the available epidemiological studies (Bates and Sizto, 1987; Lippmann, 1988). However, sulfates or other surrogates do not consistently relate to aerosol acidity (see Chapter 2) and thus these studies are limited for specific inferences regarding current ambient levels of acid aerosols. Moreover, the exposures consisted of a mixture of pollutants, making it difficult to identify the contribution of any single pollutant to the effects seen. The few epidemiological studies that have measured atmospheric acidity have often found low acid concentrations (see Section 6.2.3) or concurrently elevated ozone (Raizenne et al., 1987, 1988) and it is difficult to separate the effect of acid from ozone for the endpoint measured (pulmonary function).

The available health effects data indicate that acid aerosols have the potential to deposit and act throughout the respiratory tract. As a result, there is a broad range of health effects associated with exposure to acid aerosols from both acute and chronic exposures at various concentrations; these include effects on respiratory mechanics and symptoms, alteration of clearance and other host defense mechanisms, morphological and biochemical alterations, aggravation of existing disease or illness, and mortality. The discussion of these effects below will focus on animal and controlled human studies with exposures <1,000 $\mu g/m^3$, and pertinent epidemiological studies.

7.2.2.1 Respiratory Mechanics and Symptoms. Effects on respiratory mechanics and function can range from mild transient changes of little direct health significance to incapacitating impairment of breathing. Symptomatic effects such as coughing, wheezing, or bronchospasm also vary in severity, but at a minimum are indicative of a biological response. Mild effects in normal subjects may indicate potentially more serious responses in more sensitive subjects.

Animal, controlled human and epidemiological studies show mixed results for effects of acid aerosols on respiratory mechanics and symptoms at concentrations <1,000 μg/m^3 (Table 7-2). Most animal studies have shown no effects following acute acid sulfate exposures at these levels. Amdur and colleagues, however, have observed changes in pulmonary function in guinea pigs following 1-hour exposures to various acid sulfates alone, and in mixtures, with significant changes as low as 100 μg/m^3 H_2SO_4. Recently these investigators have examined the effect of H_2SO_4 coated ultrafine zinc oxide particles (Amdur and Chen, 1988); levels as low as 20-30 μg/m^3 H_2SO_4 delivered in this manner resulted in significant changes in pulmonary function and produced increased bronchial hypersensitivity whereas much higher levels of pure H_2SO_4 aerosol were needed to produce comparable results. Zinc oxide alone caused no effects. This suggests that the physical state of acids in pollutant mixtures is an important determinant of response.

Controlled human studies indicate that asthmatics are substantially more reactive to inhaled acid aerosols than normals; small changes in FEV_1 and thoracic resistance have been observed in adolescent asthmatics with H_2SO_4 concentrations as low as 68 μg/m^3 (Koenig et al., 1988). However, there seems to be substantial variability between studies, and even between subjects in any one study, suggesting that numerous factors may influence susceptibility.

Effects on airway reactivity have been demonstrated following acute H_2SO_4 exposures in humans (Utell et al., 1984, 1985) and chronic exposures in animals (Gearhart and Schlesinger, 1986). The development of hyperresponsive airways in otherwise normal subjects may be of special concern (see Sections 4.3 and 5.8).

Epidemiology provides suggestive, but indirect, evidence linking acute exposure to functional effects and symptoms. The available studies that have shown effects suffer from a lack of acid aerosol exposure data, or the effect of the acid component cannot be separated from the mixture of pollutants present (e.g., Raizenne et al., 1988).

Chronic exposures have produced functional effects in some animal studies (see Table 7-2). The five and one-half year chronic exposure of dogs to a mixture of H_2SO_4 and SO_2 resulted in several interesting findings (Hyde et al., 1978; Stara et al., 1980). Changes in pulmonary mechanics and structure were found at exposure levels considerably lower than in other animal studies. The functional changes became progressively more severe with time after exposure

TABLE 7-2. EFFECTS OF ACID AEROSOLS (<1,000 μg/m^3) ON RESPIRATORY MECHANICS AND SYMPTOMS

Subject/Exposure	Observed Effects/Comments	Reference
Animal Studies -- Acute		
Various animal species, exposed by various routes to H_2SO_4 and other aerosol sulfates; 30 - 1,000 μg/m^3, 0.1 - 0.6 μm for 7.5 min to 4 h	No change in the measured respiratory function parameters	Fairchild et al. (1975) Sackner et al. (1978, 1981) Schlesinger et al. (1978) (See Table 4-2)
Guinea pigs, head-only exposures, H_2SO_4, NH_4HSO_4, $(NH_4)_2SO_4$; 100 - 1,000 μg/m^3 0.13 - 1 μm for 1 h	Increase in pulmonary resistance, decrease in dynamic compliance. Lowest H_2SO_4 level (100 μg/m^3) to show function effects in animals. Also notable that $(NH_4)_2SO_4$ was more potent than NH_4HSO_4	Amdur et al. (1978a,b)
Guinea pig, head-only, H_2SO_4, NH_4HSO_4, $(NH_4)_2SO_4$; 100 - 900 μg/m^3 0.1 - 1 μm, + SO_2; 0.2 - 0.32 ppm for 1 h	Additive effect of H_2SO_4, and SO_2 on pulmonary function	Amdur (1974) Amdur et al. (1978b)
Guinea pig, head-only, H_2SO_4 coated 0.05 μm ZnO particles; 20-30 μg/m^3 equivalent H_2SO_4 for 3 h/d up to 5d	Significant reductions in total lung volume, vital capacity, and CO diffusing capacity. Effects appear to be cumulative. Hyperresponsiveness produced following a single 1h exposure	Amdur and Chen (1988)
Animal Studies -- Chronic		
Various animal species, exposed by various routes to H_2SO_4 and $(NH_4)_2SO_4$; 80 - 1,000 μg/m^3, 0.3 - 2.78 μm for 5 d to 52 wk	No change in the measured respiratory function parameters	Alarie et al. (1973) Gearhart and Schlesinger, (1986) Loscutoff et al. (1985) (See Table 4-2)
Cynomolgus monkey, chamber, H_2SO_4; 480 μg/m^3, 0.54 μm; 380 μg/m^3, 2.15 μm for 78 wk (22 - 23 h/d)	Change in the distribution of ventilation at 480 μg/m^3, increase in respiratory frequency at 380 μg/m^3	Alarie et al. (1973)
Rat, chamber, $(NH_4)_2SO_4$, NH_4NO_3; 1,000 μg/m^3, 0.4 μm for 6 h/d, 5 d/wk, 5 or 20 d	Increase in residual volume and functional residual capacity, change in the distribution of ventilation	Loscutoff et al. (1985)
Rabbit, nose-only, H_2SO_4; 250 μg/m^3, 0.3 μm for 1 h/d, 5 d/wk, up to 12 mo	Hyperresponsivity to IV acetylcholine by 4 mo; increased by 8 mo; 12 mo like 8 mo, indicating stabilization of effect	Gearhart and Schlesinger (1986)
Dogs, chamber, H_2SO_4; 760 - 890 μg/m^3, <0.5 μm alone or with SO_2; 5.1 ppm for up to 680 d (21 h/d)	Functional changes after 225 days and more changes with H_2SO_4 at 620 days. Mixture reduced DL_{CO} more than H_2SO_4 alone at 225 days	Lewis et al. (1969, 1973)
Dogs, chamber, H_2SO_4; 90 μg/^{3}, <0.5 μm + SO_2; 0.4 ppm for 16 h/d for 68 mo	No functional changes 18, 36 months; some changes at 61 months, end of exposure. 24 months after end of exposure functional losses worsened; 32-36 months after, increased total lung capacity	Hyde et al. (1978) Stara et al. (1980)
Controlled Human Studies		
Normal adult humans, exposed by various routes, at various ventilation rates, to H_2SO_4, and other sulfates; 10 - 1,000 μg/m^3 0.1 - 10 μm for 10 min to 4 h	No pulmonary function or symptom effects up to 500 μg/m^3, effects may begin at 1,000 μg/m^3	See Table 5-1 and Section 5.2

(continued on the following page)

TABLE 7-2. (continued)

Subject/Exposure	Observed Effects/Comments	Reference
Asthmatics, exposed by various routes and at various ventilation rates to H_2SO_4, and other sulfates; 10 - 1,000 μg/m³, 0.1 - 10 μm for 10 min to 4 h	Pulmonary function responses and symptoms observed in adults at 350 - 1,000 μg/m³ H_2SO_4, and in adolescents as low as 68 μg/m³. Some individuals are particularly sensitive	See Table 5-1 and Section 5.7
Asthmatics and normals, exposed by mouthpiece, at rest and with exercise, H_2SO_4, and NH_4HSO_4; 450 - 1,000 μg/m³, 0.5 - 1.0 μm for 16 min to 4 h	Increased reactivity to carbachol, generally in relation to acidity. Decrease in SG_{aw} after control carbachol exposures well correlated with decrease in SG_{aw} after H_2SO_4, exposure. Delayed increase (24 h) in reactivity noted in normals after 4 h H_2SO_4 at 450 μg/m³. 8 of 14 subjects report throat irritation 12 - 24 h post exposure	Utell et al. (1982, 1983, 1984, 1985)
Normals, at rest and with exercise, H_2SO_4, 100 to >1,000 μg/m³ in mixtures with other pollutants for 2 to 4 h	No evidence of interactive effect on respiratory function between H_2SO_4, and other pollutants	Kleinman et al. (1981) Kulle et al. (1982) Stacy et al. (1983) Kagawa (1986)
Epidemiological Studies -- Acute		
Normal and asthmatic children at summer camps, generally low levels of H^+ or H_2SO_4 (<5 μg/m³) measured	No association between lung function or symptoms and acid exposures. Some effects associated with O_3	Lippmann et al. (1983) Bock et al. (1985) Lioy et al. (1985, 1987) Franklin et al. (1985)
Children at a summer camp, some with + response to methacholine, elevated H_2SO_4, H^+ and O_3; peak levels of 47.7 mg/m³, 550 nmoles/m³ and 143 ppb respectively	Maximum decrements of 3.5% and 7% for FEV_1 and PEF respectively associated with episodes. Effects of individual pollutants not clear	Razienne et al. (1988)
School age children, pollution episodes where TSP, RSP (<3.5 μm) and SO_2 all reached >200 - 250 μg/m³ contrasted to a period with substantially lower concentrations. Acids likely present but no exposure data available	Small, but significant, reversible declines in lung function associated with measured pollutants. Still present 16 days later, but not 25.	Dassen et al. (1986)
Epidemiological Studies -- Chronic		
10,000 children age 6 - 9 in 6 U.S. cities, gradient of TSP, SO_2 and total sulfate levels (TSO_4). Annual sulfate levels ranged from 4.5 to 19.3 μg/m³. No concurrent acid measurements	Frequency of cough, bronchitis, and lower respiratory illness significantly associated with annual mean TSP and TSO_4. No difference in lung function. Prevalence of bronchitis in 4 of the 6 cities suggests a better correlation with available H^+ data than PM_{15}	Ware et al. (1986) Speizer (1988)
Various subjects, chronic exposures, pollutant variables measured include SO_2, NO_2, PM and sulfate. Acids may be present, but no quantification possible	Mixed results, some suggestion of symptom associations with the measured pollutants, and possibly functional effects. Difficulties to infer contribution of acids, if any, to the effects seen	See Section 6.3, Table 6-2, and U.S. Environmental Protection Agency (1986)

had been terminated (2 yr later), at which time emphysema was also found, implying the development of chronic, irreversible lung disease. It appears that long-term low level exposures may eventually lead to functional and morphological effects whereas other studies, limited to shorter exposure durations, have found effects only with much higher concentrations; or no effects at all.

Ware et al. (1986) from the ongoing Harvard six-city study found the frequency of cough, bronchitis, and lower respiratory illness in school age children to be significantly associated with annual mean TSP and total sulfate. Interestingly, the authors note that city-specific illness rates for Kingston and Steubenville were consistently highest--subsequent measurements of aerosol acidity (H^+) in four of the six cities show these two cities to be highest on average (Spengler et al., 1988). In addition, Speizer (1988) indicates that the subsequently measured H+ data suggest a better correlation with bronchitis prevalence than does PM_{15} in 4 of six cities with H^+ data. This qualitative information combined with evidence from animal studies (discussed below) indicates that further research is warranted to examine the role of acid aerosols in the development of chronic bronchitis. Other epidemiological studies discussed in Chapter 6 suggest that symptoms or functional changes may be associated with chronic exposures to sulfur oxides or nitrogen oxides but it is quite difficult to quantitatively relate these findings to possible acid effects in current ambient situations because there are no acid exposure data available.

7.2.2.2 Host Defense Mechanisms. The lungs have several defense mechanisms to detoxify and physically remove inhaled material. Nonspecific particle clearance mechanisms have been well-studied and appear to be sensitive to inhaled H_2SO_4 at relatively low levels (see Table 7-3). Bronchial mucociliary clearance appears to be particularly sensitive to the effects of inhaled H_2SO_4; levels as low as 100 μg/m^3 have produced alterations in mucociliary transport rates in humans and animals following either single or repeated exposures. Respiratory region clearance in rabbits has been shown to be either accelerated or retarded, suggesting a graded response that is dependent upon both exposure concentration and time (see Section 4.5.1.2b). H_2SO_4 may alter alveolar macrophage (an important defense cell of the lung) function following single or repeated exposures in animals (Naumann and Schlesinger, 1986; Schlesinger, 1987), but the data are too limited at this time to provide a

TABLE 7-3. EFFECTS OF ACID AEROSOLS (<1,000 μg/m^3) ON HOST DEFENSE MECHANISMS

Subject/Exposure	Observed Effects/Comments	Reference
Animal Studies -- Acute to Subchronic		
Various animal species, various routes of exposure to aerosol sulfates; 200 - 1,000 μg/m^3 1 h to 6 h.	Mixed results on tracheal clearance, generally no effect. Particle size may be important variable	See Table 4-4
Rabbits and donkeys, various routes of exposure to H_2SO_4; 100 to >1,000 μg/m^3, 0.3 - 0.4 μm for 1 h	Speeding (at lower concentrations) and slowing (at higher concentrations) of bronchial clearance. Effects related to acidity of sulfates, but NH_4HSO_4 and $(NH_4)_2SO_4$ show no effects <1,000 μg/m^3. Repeated exposures may lead to persistent changes	Chen and Schlesinger (1983) Schlesinger et al. (1978, 1984) Schlesinger (1984, 1988)
Rabbits, nose only, H_2SO_4; 1,000 μg/m^3, 0.3 μm for 1 h	Respiratory region clearance accelerated. Alveolar macrophage surface adherence retarded, phagocytosis enhanced	Naumann and Schlesinger (1986)
Rabbits, nose only, H_2SO_4; 500 μg/m^3, 0.3 μm, for 2 h/d up to 13 d	Alveolar macrophage counts increased after 2 exposures, return to control level thereafter; random mobility decreased after 6 and 13 exposures	Schlesinger (1987)
Mice, various routes of exposure to acid sulfates; 365 - >1,000 μg/m^3, 0.06 - <1.0 μm for 2 h or 2 h/d, 5d	No effect on bacterial infectivity	Gardner et al. (1977) Grose et al. (1982) See also Table 4-6
Mice, chamber, H_2SO_4; 900 μg/m^3, 0.2 μm for 2 h immediately after 3 h O_3 exposure, 0.1 ppm	Additive increase in bacterial infectivity. No difference from control when H_2SO_4 was administered prior to O_3. Neither pollutant alone caused a significant increase in infectivity	Gardner et al. (1977)
Mice, chamber, H_2SO_4; 240 - 480 μg/m^3, 0.2 μm + O_3, 0.1 ppm for 3 h	Synergistic effects on bacterial infectivity	Grose et al. (1982)
Animal Studies -- Chronic		
Rabbits and donkeys, various routes of exposure to H_2SO_4; 100 - 500 μg/m^3, 0.3 - 0.5 μm for 1 h/d, 5 d/wk, up to 12 mo	Speeding or slowing of bronchial clearance. Effects may be progressive and persistent	Schlesinger et al. (1979, 1983) Gearhart and Schlesinger (1988)
Rabbits, nose only, H_2SO_4; 250 μg/m^3, 0.3 μm for 1 h/d, 5 d/wk, up to 240 d or 500 μg/m^3 for 2 h/d, 14 d	Respiratory region clearance accelerated at 250 μg/m^3, retarded at 500 μg/m^3	Schlesinger and Gearhart (1986, 1987)
Controlled Human Studies		
Normal and asthmatic subjects, nasal mask at rest, H_2SO_4; 100 - 1,000 μg/m^3, 0.5 μm, for 1 h - 2 h	No effect on tracheal mucociliary clearance. Bronchial mucociliary clearance accelerated at low concentrations, retarded at high. Small airway clearances retarded at all concentrations, probably related to regional deposition of acid. Longer exposure (2 h) produced greater effect. Lower baseline clearance of asthmatics may place them at greater risk	Leikauf et al. (1981, 1984) Spektor et al. (1985, 1988)

complete understanding of the cellular mechanisms that may underlie changes in respiratory region clearance.

The pathogenic implications of altered clearance mechanisms have been discussed previously (see Sections 4.5, 4.8) and, in short, the significance of transient alterations after short-term exposure is unclear, but such changes may be an indication of a lung defense response. On the other hand, persistent impairment of clearance may lead to the inception or progression of chronic respiratory disease, suggesting a plausible link between inhaled acid aerosols and respiratory pathology. For example, Lippmann et al. (1982) emphasize the similarities between clearance effects of cigarette smoke and H_2SO_4; smoking has a well established role in the development of chronic bronchitis. Lippmann et al. (1987) recently examined this evidence and other data suggesting a possible link between H_2SO_4 exposure and the pathogenesis of chronic bronchitis.

Few other animal studies have provided evidence to indicate that acid aerosols may compromise lung defense mechanisms. Acid aerosols are apparently not very effective in enhancing susceptibility to bacterial-mediated respiratory disease in mice (see Table 4-6), but two studies indicate significant interactions with ozone (Gardner et al., 1977; Grose et al., 1982). As with other endpoints, the effect of mixtures on infectivity needs further examination. No animal data directly examine the effects of acid on viral infectivity. Little is known about the effects of acid aerosols on immunologic defense mechanisms (see Section 4.5.2).

7.2.2.3 Morphological and Biochemical Alterations. Morphological or biochemical changes are often detected by invasive techniques and hence most data for acid aerosols are derived from controlled animal tests. Table 7-4 presents relevant studies with exposures <1,000 $\mu g/m^3$.

Few effects have been demonstrated in animal studies following acute exposures at levels <1,000 $\mu g/m^3$ (see Section 4.4). This may be due in part to different sensitivities of various species or the endpoints studied. However, three hour exposures to low levels of H_2SO_4 delivered as a coating on ultrafine zinc oxide particles have produced an increase in the protein content of pulmonary lavage fluid and an increase in neutrophils (Amdur and Chen, 1988), indicating tissue damage and an inflammatory response. Amdur and colleagues have not yet done animal exposures to coal combustion products, but suggest that the response produced by the prototype acid coated zinc oxide aerosols may

TABLE 7-4. EFFECTS OF ACID AEROSOLS (<1,000 µg/m³) ON MORPHOLOGICAL AND BIOCHEMICAL INDICES

Subject/Exposure	Observed Effects/Comments	Reference
Animal Studies -- Acute to Subchronic		
Rat, chamber, H_2SO_4; 40 to 1,000 µg/m³, 0.4 - 0.5 µm with O_3, 0.12 - 0.64 ppm or NO_2, 4.7 - 4.9 ppm; $(NH_4)_2SO_4$; 484 µg/m³, 0.53 µm with O_3, 0.99 ppm for 6 h to 9 d	No effects of H_2SO_4 alone on the measured biochemical endpoints. Synergism with O_3 on lavageable and tissue protein content of lungs and on collagen synthesis rate. H_2SO_4 as low as 40 µg/m³ acts synergistically with O_3 in altering collagen synthesis rate and total lung protein content	Warren and Last (1987) Last and Warren (1987) Last et al. (1986)
Guinea pigs, head only, H_2SO_4 coated 0.05 µm ZnO particles; 20 - 30 µg/m³ equivalent H_2SO_4, for 3 h/d up to 5 d	Lavageable protein content increased substantially on 1st and 3rd days of exposure, slightly on 4th and 5th. Neutrophils also elevated, peak after 3rd day	Amdur and Chen (1988)
Animal Studies -- Chronic		
Dog, chamber, H_2SO_4; 889 µg/m³, <0.5 µm for for 21 h/d, 680 d	Some interstitial inflammation, but no overall clear-cut changes	Lewis et al. (1973)
Dogs, chamber, H_2SO_4; 90 µg/m³, <0.5 µm, + SO_2; 0.4 ppm for 16 h/d for 68 mo	32-36 months after exposure ended a number of morphological changes, including loss of cilia in conducting airways, possible bronchiolar cell hyperplasia, loss of interalveolar septa, enlarged air spaces, increase in number and site interalveolar pores, suggestive of emphysema	Hyde et al. (1978) Stara et al. (1980)
Monkey, chamber, H_2SO_4; 100 - 1,000 µg/m³, <1 µm or 1 - 4 µm, alone or with: SO_2; 1 ppm and/or fly ash; 400 - 550 µg/m³ for 18 mo	Slight but definite histopathological effects; small and variable at 100 µg/m³, more pronounced at 1,000 µg/m³ H_2SO_4. Effects included goblet cell hypertrophy and hyperplasia, bronchiolar epithelial hyperplasia, and thickening of the walls of respiratory bronchioles. Deleterious effects of mixtures attributable to the H_2SO_4	Alarie et al. (1973, 1975)
Rabbits, oral tube or nose only, H_2SO_4; 250 - 500 µg/m³, 0.3 µm for 1 h/d, 5 d/wk, up to 52 wk	Increased epithelial thickness in small airways, increase in airway secretory cell number, increase in number of small airways	Schlesinger et al. (1983) Gearhart and Schlesinger (1988)
Hamster, chamber, $(NH_4)_2SO_4$; 187 µg/m³, 0.3 µm for 6 h/d, 5 d/wk, 15 wk	Emphysematic lesions	Godleski et al. (1984)
Controlled Human Studies		
Healthy adults, chamber, at rest and with exercise, H_2SO_4; 100 µg/m³, 0.5 µm for 4 h on 2 consecutive days	No effect of H_2SO_4 on several measured blood parameters	Chaney et al. (1980a,b)

have considerable relevance for such exposures. Much higher levels of pure H_2SO_4 droplets were required to elicit similar responses; the levels of zinc oxide used alone caused no effects.

Chronic or repeated peak exposures to acid aerosols have produced morphological changes in animals (see Table 7-4). The dog study of Hyde et al. (1978) provides unique insights into extended exposures (5½ yr) to a mixture of sulfur oxides. Several morphological changes were observed. The authors consider these changes to be analogous to an incipient stage of emphysema. Stara et al. (1980) found that changes in pulmonary function of the dogs correlated well with the morphological effects. Since the changes in pulmonary function were progressive over the post-exposure period, it is likely that morphological changes were also progressive. There are several points to consider to apply the dog studies to real world exposures (see U.S. Environmental Protection Agency 1982a,b) including the possibility that actual acid exposures may have been lower than 90 $\mu g/m^3$ due to neutralization by chamber ammonia. Progressive effects were also found by Gearhart and Schlesinger (1988), on tracheobronchial clearance in rabbits exposed to H_2SO_4, that continued even after exposure ceased, again implying progressive, irreversible effects.

It seems reasonable to attribute most of the deep lung effects in the dog studies, and other studies with SO_2/H_2SO_4 mixtures, to the acid component, based on the probability of deep lung deposition of the aerosol. If the dog studies of Hyde et al. (1978) and Lewis et al. (1973) can be directly compared, they indicate that morphological effects of the SO_x mixture are more pronounced with extended lower level exposure than with much higher concentrations for a shorter exposure period.

The studies of rabbits (see Table 7-4) provide evidence that low level (250 $\mu g/m^3$) chronic exposure to H_2SO_4 results in hypertrophy and/or hyperplasia of mucus secretory cells in the epithelium; these alterations may extend to the small bronchi and bronchioles, where secretary cells are normally rare or absent (Gearhart and Schlesinger, 1988). These findings are consistent with the results of Alarie et al. (1973, 1975) for monkeys chronically exposed to mixtures of H_2SO_4 and SO_2. One result of these morphological alterations may be an increase in mucus loading of these airways, which is a possible factor in the pathogenesis of obstructive lung disease such as chronic bronchitis.

Low levels of H_2SO_4 (40 $\mu g/m^3$) have been shown to react synergistically with ozone in altering biochemical indices (Warren and Last, 1987). In this case, the disease associated with these changes is speculated to be pulmonary fibrosis (Last et al., 1983). As mentioned earlier, acid aerosols will frequently be associated with elevated ozone levels, and there is a need for further research addressing pollutant mixtures.

The limited data on morphological and biochemical endpoints restricts quantitative risk assessment of health effects occurring at current ambient levels of acid aerosols, but such data are critical to begin to understand the range of potential health effects as well as the mechanisms of toxicity of acid aerosols from which to focus future work.

7.2.2.4 Aggravation of Existing Disease or Illness. Evidence linking acid aerosol exposure to aggravation of existing disease or illness is reviewed in Table 7-5. As is evident, animal data are limited. However, since bronchoconstriction may be an important mechanism by which acid aerosols aggravate existing respiratory disease, animal and human clinical studies indicating effects on respiratory mechanics are relevant here (see Table 7-2). In any event, controlled human studies indicate that asthmatics are markedly more sensitive to inhaled acid aerosols, but epidemiology provides evidence that other individuals may be particularly sensitive to air pollution that includes acid aerosols.

Lawther et al. (1970), in a classic study of chest clinic patients (mostly bronchitics, but some patients had asthma or emphysema), found day-to-day changes in health status to depend on daily variations in London pollution (SO_2 and British Smoke), measured at seven sampling sites. (This study is discussed at some length in U.S. Environmental Protection Agency 1982a,b.) Interestingly, daily sulfuric acid, measured from one central site beginning in the winter of 1963, was most strongly correlated with effects in a group of patients for the winter of 1964-1965, but less so for 1967-1968. The authors suggest that sulfuric acid may be of special interest as a respiratory irritant. Pollution levels had declined substantially from previous years by this time, although still quite high compared to current U.S. conditions.

The ongoing correlational study of Bates and Sizto (1983, 1986, 1987) relating hospital admissions in Southern Ontario to air pollutant levels is of interest for more contemporary exposures. These analyses demonstrate a consistent summer relationship between sulfates, ozone and temperature, and acute respiratory admissions with or without asthma (see Section 6.2.4). There

TABLE 7-5. EFFECTS OF ACID AEROSOLS ON INDIVIDUALS WITH EXISTING DISEASE OR ILLNESS

Subject/Exposure	Observed Effects/Comments	Reference
Animal Studies--Chronic		
Rats and guinea pigs, elastase-induced pulmonary emphysema, $(NH_4)_2SO_4$ or NH_4NO_3; 1,000 µg/m³, 6 h/d, 5 d/wk, 20 d	Disease state did not enhance the effect of the aerosols in altering pulmonary function or lung structure	Loscutoff et al. (1985) Busch et al. (1984, 1986)
Dogs, lungs impaired by prior NO_2 exposure, H_2SO_4; 889 µg/m³, 21 h/d, 620 d	Impairment by NO_2 did not enhance effect of H_2SO_4 on pulmonary function	Lewis et al. (1973)
Controlled Human Studies		
Asthmatics, various exposures to acid aerosols	Asthmatics appear to be markedly more susceptible to the effects of inhaled acids	See Table 5-1 and and Section 5.7
Epidemiological Studies--Acute		
Daily (and hourly) fluctuations in pollution mix in London dominated by high PM and SO_2 levels from fossil fuel combustion. Acid present, some limited measurements available.	Exacerbation of condition of patients with severe bronchitis and emphysema correlated with daily variations in pollution	Lawther et al. (1970)
Hourly mean levels of O_3, SO_2, coefficient of haze, and 24 h mean sulfate. Evidence for elevated free H^+ in the region.	Consistent summer relationship between sulfates, O_3 and temperature, and hospital respiratory admissions with or without asthma. Consistent lack of association with non-respiratory conditions. Aerosol sulfates explain the highest percentage of variance in respiratory admissions in the summer.	Bates and Sizto (1983, 1986, 1987)
Regional event in Europe (Germany), high levels of SO_2, NO_2, PM measured, peak levels of: 830, 410, and 600 µg/m³ respectively were recorded. Acids likely present but no exposure data available	Increase in several morbidity measures resulting from the event. Effects more pronounced for cardiovascular disease than respiratory disease	Wichmann et al. (1988)

is a continuing lack of association of these variables with non-respiratory conditions. Bates and Sitzo (1987) indicate that it is not clear whether the association of increased respiratory admissions can be ascribed to ozone or sulfates (the only two pollutants monitored on a regular basis which show a consistent association) or possibly to some unmeasured species that "travels" with them over the region in the summer. Recent monitoring efforts in the area indicate peaks of H^+ of small particle size (about 0.2 µm) on days when ozone and sulfate levels were elevated. These data are interesting and are of particular relevance for possible health effects at current ambient levels of acid aerosols, but as yet, the hypothesis that hospital admissions in this area are more readily attributed to acid aerosols is untested because of a lack of H+ data.

A significant pollution event occurred in Europe in January 1985 (see Section 6.2.2). Notable increases in several measures of morbidity were observed in Germany (Wichmann et al., 1988), especially for cardiovascular disease. Acid levels for the study area were not determined, but the levels of PM, SO_2 and NO_2 were quite high.

The available epidemiological studies, taken as a whole, suggest that certain individuals or groups may be sensitive to air pollution that includes acid aerosols, but ascribing the observed health effects to acid exposure is difficult because of a lack of sufficient ambient acid measurements.

7.2.2.5 Mortality. Evidence linking mortality to acid aerosol exposures at concentrations <1,000 µg/m^3 is limited to epidemiological studies (Table 7-6); animal studies of H_2SO_4 do not indicate mortality effects at these levels. This strongly suggests that a mixture of pollutants may be important or that individual sensitivity is crucial.

Excess mortality clearly resulted from acute exposures during the severe pollution episodes of Meuse Valley, Donora, and London. Of greater relevance for the present discussion, however, are studies such as those of Schwartz and Marcus (1986) that show mortality associations in London continuing to periods of much lower pollution, with no evidence of a threshold, and a preliminary analysis of the London mortality data for which daily acid aerosol measurements are available from a central site (Thurston et al., 1988). The results of the latter study indicate that the log of acid aerosol concentrations is more strongly associated with raw total mortality in bivariate analyses than is British Smoke (BS) or SO_2. The H_2SO_4 results may be more readily applied to

TABLE 7-6. MORTALITY EFFECTS OF ACID AEROSOLS

Subject/Exposure	Observed Effects/Comments	Reference
Animal Studies		
Mortality in animals not demonstrated until acid levels well in excess of 1,000 μg/m^3		
Epidemiological Studies-- Acute		
Severe pollution episodes characterized by extremely high levels of a diverse mix of pollutants, dominated by emissions from combustion of fossil fuel. High acid levels likely present but not quantified	Excess mortality clearly associated with exposure to these short-term extreme pollution episodes. Many of the deaths were among people with preexisting respiratory and cardiovascular conditions and the elderly. Difficult to separate effects of pollutants, weather and other variables	Firket (1931) Schrenk et al. (1949) U.K. Ministry of Health (1954) Martin and Bradley (1960)
Elevated levels of PM (BS) and SO_2 in London largely from combustion of fossil fuels. One site with H_2SO_4 (apparent) measurements from 1954-1964, peak daily and hourly levels of 347 μg/m^3 and 678 μg/m^3, respectively	Consistent association between BS and SO_2 and mortality in 14 winters (1958-1972) spanning a period when pollution in London declined substantially. No indication of a threshold at lower BS concentrations (e.g., <150 μg/m^3). Preliminary analysis of available acid data indicates association between log of acid and mortality	Mazumdar et al. (1982) Ostro (1984) Schwartz and Marcus (1986) Thurston et al. (1988)
Time-series analysis of 14 years (1963-1976) of daily mortality in New York City. Particles measures, but no acid data available for analysis	Significant associations between mortality and particle concentrations (indicated by coefficient of haze and visibility readings). Limited data indicate very low levels of strong acid present for New York City (Tanner et al., 1981)	Ozkaynak and Spengler (1985)
Regional episode in Europe (Germany), SO_2, NO_2, PM measured, levels reaching 830, 410, 600 μg/m^3 respectively, no acid exposure data	Increase mortality associated with the pollution episode. Difficult to separate effects of the various pollutants	Wichmann et al. (1988)
Epidemiological Studies -- Chronic		
Ecological analyses across standard metropolitan statistical area (SMSAs), pollutants measures include TSP, PM, and sulfates chronic exposure. No acid data included	Mixed results, providing limited conclusions regarding long-term exposure and mortality. Analyses sensitive to inclusion/exclusion of different variables. Sulfate shows significant correlation with mortality in some analyses	Lave and Seskin (1972, 1977) Lipfert (1984) Chappie and Lave (1982) See also U.S. Environmental Protection Agency (1982a,b, 1986)
Ecological analyses across SMSAs, pollutant measures include TSP, IP (<15 μm), FP (<2.5 μm) and sulfate; chronic exposures. No acid data included	FP and sulfate consistently and significantly associated with SMSA specific total annual mortality rates	Ozkaynak and Spengler (1985) Ozkaynak and Thurston (1987)

other environments than is the case for existing BS results, yet differences in the composition and levels of pollutants between current conditions in the U.S. and those in London at the time the mortality data were gathered still limits the applicability of the London mortality data to contemporary North American atmospheres.

A more recent study (Ozkaynak and Spengler, 1985) provides qualitative support for an association between daily mortality and particle concentrations in nearly contemporary U.S. atmospheres (14 years of New York city data, 1963-1976). In this case, the mortality associations, although correlated with plausible acid aerosol surrogate measures (coefficient of haze and atmospheric visibility readings), do not appear to support possible acid aerosol effects; limited data available for the New York City region show very low levels of strong acid present for urban New York City, indicating substantial neutralization of acid sulfates from urban ammonia sources (Tanner et al., 1981).

The recent study by Wichmann et al. (1988) indicated increased mortality following a European pollution episode, but the levels of several pollutants were quite high and it is not clear what part acid aerosols may have played, if any, in this event.

Several ecological analyses have attempted to relate mortality rates to chronic exposures of sulfate and other pollution measures (see Table 7-6 and U.S. Environmental Protection Agency, 1982a,b, 1986). There are significant problems with these kinds of analyses that limit both quantitative and qualitative conclusions (see U.S. Environmental Protection Agency, 1986). The more recent cross-sectional analyses of Ozkaynak and Spengler (1985) and Ozkaynak and Thurston (1987) address some of these problems. The predictors of mortality due to air pollution examined in their analyses were expressed in terms of four aerosol pollutant measures: TSP, IP (inhalable particles), FP (fine particles), and SO_4^{2-} (sulfate). Among these, FP and SO_4^{2-} were most consistently and significantly associated with the reported SMSA-specific total annual mortality rates, while TSP and IP were often nonsignificant predictors of mortality. This is consistent with a hypothesis that aerosol acidity may be a stronger predictor of total mortality because the fraction of H^+ in terms of mass concentration at a particular time and place would rank SO_4^{2-} > FP > IP > TSP. However, as noted earlier, sulfate or other surrogate measurements do not consistently relate to aerosol acidity and, without historical data, a acid-mortality hypothesis cannot be examined for these data.

7.2.2.6 Summary of Health Effects. As is evident, there are many possible health effects associated with acid aerosols, both with acute and chronic exposures, but the available animal and controlled human data to assess concentration-response relationships are limited to a small set of studies in which exposures are relatively low (<250 μg/m^3); few concentration-response studies have been performed, and no studies are available that report effects of acid aerosol alone at levels in the range of ambient concentrations. However, chronic studies of ambient acid levels using sensitive measurement techniques have not been performed. Thus the no measurable effect level is not adequately defined for risk assessment purposes. At present, epidemiology provides no clear quantitative relationships because of a lack of sufficient ambient acid measurements by which to define exposure-response effects levels.

Several factors that are not well understood at this time influence concentration-response relationships of acid aerosols, and controlled studies, therefore, may not yet have adequately characterized potential effects in the general population. These factors include:

- Acutely sensitive groups may not yet be sufficiently identified. Data from animal studies (e.g., Schlesinger et al., 1979; Wolff et al., 1979) and human clinical studies (e.g., Avol et al., 1979; Utell et al., 1983) suggest that certain individuals, even within selected subgroups, may be particularly sensitive to acid aerosols. Where possible, these "hyperresponders" should receive increased study to allow extrapolation to populations at greatest risk in the general public. For chronic exposures it may be difficult to identify a sensitive group, rather all sufficiently exposed people may be at risk.

- Concentration x time relationships have not yet been fully studied. Spengler et al. (1988) compare estimated dose between the controlled exposure studies of Koenig et al. (1983) (100 μg/m^3, 40 min. exposure), Utell et al. (1983) (450 μg/m^3, 16 min. exposure), and a 1-hour peak ambient exposure at an outdoor camp in Southern Ontario. By including variables on concentration, aerosol retention, minute ventilation and time, Spengler et al. calculate that children engaged in summertime outdoor activities can experience H^+ doses comparable to effects levels in controlled human studies. Few animal or controlled human data are available to assess CxT relationships.

- Delayed or progressive effects may have been missed. There are some data to suggest that such effects may occur including delayed development of airway hypersensitivity (Utell et al., 1985) and progressive functional and morphological effects (Stara et al., 1980; Gearhart and Schlesinger, 1988).

- Breathing mode (see Chapter 3) and breathing mechanics may significantly alter deposition (and thus possible response) of acid aerosols. For example, exercise exacerbates the effects of inhaled H_2SO_4 (Utell et al., 1986). Additionally, disease states (e.g., asthma, bronchitis) or age-related factors influence deposition (see U.S. Environmental Protection Agency, 1982a,b, 1986).

- Oral and respiratory tract ammonia may be critical in neutralizing inhaled acids and mitigating responses (Larson et al., 1977; Utell et al., 1986; see also Section 3.4). In addition, reduced buffering and H^+ ion absorption capacity of airway mucus may predispose certain individuals to effects of inhaled acids (Holma, 1985, 1988).

- Few data on ambient particle size are available. Animal data indicate that particle size influences the potency and temporal pattern of response (see Chapter 4); controlled human exposure data indicate that submicrometer particles are more effective per mass in altering respiratory mechanics than large particles more typical at acid fogs (see Table 5-1). Regional mucociliary clearance effects are apparently related to regional deposition of H^+ and hence particle size (Lippmann, 1985). In addition, deposition depends on hydrated, rather than initial, particle size, but the net effect of hygroscopicity is not adequately understood (see Section 3.3).

- There is inconclusive evidence on the effect of mixtures of pollutants. Levels as low as 40 $\mu g/m^3$ H_2SO_4 may act synergistically with O_3 (Warren and Last, 1987); as yet, other animal or controlled human studies have shown minimal effects due to H_2SO_4 at low levels in mixtures (see Sections 4.6 and 5.4). Acid aerosols will often be associated with multiple pollutants, especially O_3. Epidemiology studies show effects in the presence of elevated levels of acids and ozone (Raizenne et al., 1987, 1988).

In summary, the available information derived from animal and controlled human studies clearly indicates that exposure to acid aerosols at high enough concentrations can produce health effects of concern, particularly in sensitive subgroups of the population and after chronic exposure. The bulk of these studies, however, have examined H_2SO_4 exposures. Data for other acid species and mixtures are extremely limited. The effects seen range from mild and transient changes, such as small, reversible functional effects in exercising asthmatics, to more substantial effects that may have acute or chronic health consequences, such as persistently altered clearance and structural changes that may be suggestive of chronic bronchitis. It is less clear, however, whether effects are occurring at current peak ambient levels. The controlled human studies have not yet demonstrated effects of acid aerosols at concentrations within the known range of ambient concentrations. Animal studies indicating the development of chronic, irreversible lung disease require replication and extension to lower concentrations for adequate risk assessment. Most available community epidemiological studies, while indicating that effects consistent with those observed in animal and human clinical studies may occur at current ambient exposures, suffer significant limitations because of their reliance on surrogate pollutant indices. The lack of direct measurement data for acid aerosols limits the value of these studies for purposes of assessing the health risks posed by current ambient levels of acid aerosols. The few epidemiological studies that do have direct acid measurements generally recorded low acid levels (see Section 6.2.3) or, where acid levels were elevated, ozone was also elevated (Raizenne et al., 1987, 1988) and the contribution of the acid component for affecting endpoint measured (pulmonary function) is not clear. Finally, there are several factors that may significantly influence concentration-response relationships that are not completely understood. It is difficult, therefore, to make judgements at this time regarding the level of protection provided by existing NAAQS for this particular group of pollutants.

7.2.3 Sources of Acid Aerosols

A major consideration in reaching a decision to list a pollutant for regulation under Sections 108 and 109 of the Act is whether the pollutant is derived from numerous or diverse mobile or stationary sources.

As discussed in Chapter 2, acid aerosols are principally transformation products of SO_2 and NO_2. Other acids such as HCl and some organic acids are generally minor contributors to ambient strong acid aerosols.

The major precursors of acid aerosols (SO_2, NO_2) are emitted from ubiquitous sources. SO_2 is emitted principally from combustion or processing of sulfur-containing fossil fuels and ores. Emissions of NO_x result mainly from combustion of fossil fuels such as coal, oil, or gasoline from mobile or stationary sources.

Both SO_2 and NO_2 are currently regulated under Sections 108 and 109 of the Act.

7.2.4 Implications of Listing Acid Aerosols

While the subject is not a major focus of this paper, it is important to recognize and briefly consider the implications of a decision to list acid aerosols as a criteria air pollutant when assessing the available data. Once a pollutant is listed, Sections 108 and 109 of the Act require issuance of air quality criteria and the proposal of air quality standards within 12 months.

The practical effect of these requirements is that the scientific and technical data available at the time a decision to list is made must be sufficiently developed to serve as the basis for criteria and standards. Therefore, when assessing the existing data on acid aerosols, consideration should also be given to whether it is adequate to provide the kind and amount of technical information needed to:

1) define a pollutant indicator and associated measurement methodology;
2) select appropriate averaging times and forms for standards; and
3) establish appropriate standard levels.

7.3 ALTERNATIVE APPROACHES FOR A LISTING DECISION

The focus of this chapter has been on those critical elements that EPA staff believe should be considered in a listing decision. The major considerations included: 1) characterizing and defining acid aerosols as a pollutant entity for purposes of regulation; 2) possible health effects of acid aerosols at current ambient levels; and 3) the sources of acid aerosols. Each of these elements is of central relevance for listing decisions under Section 108 of the Act.

The key findings of this assessment are summarized below:

1) Limited data are available to characterize and define acid aerosols. Several species may contribute to aerosol acidity but acid sulfates appear to be the primary component. At present, acid aerosols have not been defined as a single pollutant entity; rather different measures and measurement techniques have been employed. In addition, few data are available to quantify ambient acid levels and acid events, thus possible human exposures are not well documented.

2) Available information from animal and controlled human studies is limited, but clearly indicates that at high enough concentrations acid aerosols can produce health effects of concern, particularly in sensitive subgroups of the population and after chronic exposure. It is less clear, however, whether effects of concern are occurring at current peak ambient levels. Controlled human studies have not yet demonstrated effects of acid aerosols within the range of known ambient concentrations. Animal studies indicate chronic, irreversible effects but require replication and extension to lower concentrations for adequate risk assessment. Most of the available community epidemiological studies, while indicating that effects consistent with those observed in animal and controlled human studies may occur at current ambient levels, have significant limitations because of their reliance on surrogate pollutant indices. The few studies with concurrent acid measurements provide limited information for the specific importance of the acid component of the atmosphere. Epidemiological studies, therefore, have limited value at this time for assessing the health risk associated with current ambient levels of acid aerosols.

3) The principal precursors (SO_2 and NO_2) of acid aerosols are emitted from numerous and diverse sources.

As indicated earlier, the central question to be addressed in this review is whether the available scientific and technical information provides sufficient and compelling evidence to proceed with the separate listing of acid aerosols. When assessing the adequacy of the available data in light of this question, consideration must be given to the fact that acid aerosols and their principal precursors are currently regulated to varying degrees by the existing national ambient air quality standards (NAAQS) for particulate matter, sulfur oxides and nitrogen oxides. Thus, a decision to list acid aerosols should be based on a clearly established need to provide additional public health protection beyond that afforded by the current NAAQS. Finally, the implications of a listing decision should be considered. Because the statutory schedule requires the issuance of air quality criteria and standards within 12 months of such a decision, the available scientific and technical information must be sufficient to serve as the basis for criteria and provide the kind and amount of technical information needed to set standards.

Given the above information, three alternative courses of action should be considered.

1) Recommend that the Administrator consider listing acid aerosols under Section 108 of the Act. This implies a judgement that the available health effects information is compelling enough to require additional protection beyond the current NAAQS. Within 12 months of a listing decision, EPA must issue air quality criteria and propose standards.

2) Recommend that the Administrator not consider listing acid aerosols under Section 108. The available health effects information as well as any new research would be considered during the next review of the particulate matter standards.

3) Recommend that the Administrator defer judgement regarding action to list acid aerosols pending further research on the critical needs identified in Chapter 8.

Based on the staff's assessment of the available information, it appears that the scientific and technical basis is not sufficient at this time to proceed to list acid aerosols as a criteria pollutant and to develop a national ambient air quality standard. The most convincing data clearly indicate that at high enough concentrations, health effects of concern are associated with exposure to acid aerosols, but these data do not show effects within the range of known ambient levels. Nevertheless, data of a more qualitative nature suggest some risk at ambient levels, but are not sufficient for reaching any firm conclusions regarding the health risks associated with current ambient exposures. This uncertainty regarding health risks at ambient exposures, coupled with the need to better characterize and define acid aerosols, suggests that it is difficult to make conclusions regarding the level of protection provided by existing NAAQS and therefore adoption of either alternative 1) or 2) would be premature. With the concern arising from what is known, the staff believes that additional research is warranted and therefore the most appropriate course of action would be to recommend that the Administrator defer judgement pending further research on the critical needs identified in Chapter 8.

7.4 REFERENCES

Alarie, Y.; Busey, W. M.; Krumm, A. A.; Ulrich, C. E. (1973) Long-term continuous exposure to sulfuric acid mist in cynomolgus monkeys and guinea pigs. Arch. Environ. Health 27: 16-24.

Alarie, Y. C.; Krumm, A. A.; Busey, W. M.; Ulrich, C. E.; Kantz, R. J., II. (1975) Long-term exposure to sulfur dioxide, sulfuric acid mist, fly ash, and their mixtures: results of studies in monkeys and guinea pigs. Arch. Environ. Health 30: 254-262.

Amdur, M. O. (1974) 1974 Cummings memorial lecture: the long road from Donora. Am. Ind. Hyg. Assoc. J. 35: 589-597.

Amdur, M. O.; Chen, L. C. (1988) Furnace generated acid aerosols: speciation and pulmonary effects. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Amdur, M. O.; Dubriel, M.; Creasia, D. A. (1978a) Respiratory response of guinea pigs to low levels of sulfuric acid. Environ. Res. 15: 418-423.

Amdur, M. O.; Bayles, J.; Ugro, V.; Underhill, D. W. (1978b) Comparative irritant potency of sulfate salts. Environ. Res. 16: 1-8.

Aranyi, C.; Vana, S. C.; Thomas, P. T.; Bradof, J. N.; Fenters, J. D.; Graham, J. A.; Miller, F. J. (1983) Effects of subchronic exposure to a mixture of O_3, SO_2 and $(NH_4)_2SO_4$ on host defenses of mice. J. Toxicol. Environ. Health 12: 55-71.

Avol, E. L.; Jones, M. P.; Bailey, R. M.; Chang, N.-M. N.; Kleinman, M. T.; Linn, W. S.; Bell, K. A.; Hackney, J. D. (1979) Controlled exposures of human volunteers to sulfate aerosols: health effects and aerosol characterization. Am. Rev. Respir. Dis. 120: 319-327.

Bates, D. V.; Sizto, R. (1983) Relationship between air pollutant levels and hospital admissions in Southern Ontario. Can. J. Pub. Health 74: 117-122.

Bates, D. V.; Sizto, R. (1986) A study of hospital admissions and air pollutants in southern Ontario. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment and control strategies: proceedings of the 2nd US-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 767-777.

Bates, D. V.; Sizto, R. (1987) Air pollution and hospital admissions in Southern Ontario: the acid summer haze effect. Environ. Res. 43: 317-331.

Bock, N.; Lippmann, M.; Lioy, P.; Munoz, A.; Speizer, F. E. (1985) The effects of ozone on the pulmonary function of children. In: Lee, S. D. Evaluation of the scientific basis for ozone/oxidants standards: proceedings of an APCA international specialty conference; November 1984; Houston, TX. Pittsburgh, PA: Air Pollution Control Association; pp. 297-308.

Busch, R. H.; Buschbom, R. L.; Cannon, W. C.; Lauhala, K. E.; Miller, F. J.; Graham, J. A.; Smith, L. G. (1984) Effects of ammonium sulfate aerosol exposure on lung structure of normal and elastase-impaired rats and guinea pigs. Environ. Res. 33: 454-472.

Busch, R. H.; Buschbom, R. L.; Cannon, W. C.; Lauhala, K. E.; Miller, F. J.; Graham, J. A.; Smith, L. G. (1986) Effects of ammonium nitrate aerosol exposure on lung structure of normal and elastase-impaired rats and guinea pigs. Environ. Res. 39: 237-252.

Chaney, S.; Blomquist, W.; Muller, K.; DeWitt, P. (1980a) Biochemical effects of sulfuric acid mist inhalation by human subjects while at rest. Arch. Environ. Health 35: 270-275.

Chaney, S.; Blomquist, W.; Muller, K.; Goldstein, G. (1980b) Biochemical changes in humans upon exposure to sulfuric acid aerosol and exercise. Arch. Environ. Health 35: 211-216.

Chappie, M.; Lave, L. (1982) The health effects of air pollution: a reanalysis. J. Urban Econ. 12: 346-376.

Chen, L. C.; Schlesinger, R. B. (1983) Response of the bronchial mucociliary clearance system in rabbits to inhaled sulfite and sulfuric acid aerosols. Toxicol. Appl. Pharmacol. 71: 123-131.

Cobourn, W. G.; Husar, R. B. (1982) Diurnal and seasonal patterns of particulate sulfur and sulfuric acid in St. Louis, July 1977-June 1978. Atmos. Environ. 16: 1441-1450.

Dassen, W.; Brunekreef, B.; Hoek, G.; Hofschreuder, P.; Staatsen, B.; de Groot, H.; Schouten, E.; Biersteker, K. (1986) Decline in children's pulmonary function during an air pollution episode. J. Air Pollut. Control Assoc. 36: 1223-1227.

Fairchild, G. A.; Stultz, S.; Coffin, D. L. (1975) Sulfuric acid effect on the deposition of radioactive aerosol in the respiratory tract of guinea pigs. Am. Ind. Hyg. Assoc. J. 36: 584-594.

Ferek, R. J.; Lazrus, A. L.; Haagenson, P. L.; Winchester, J. W. (1983) Strong and weak acidity of aerosols collected over the northeastern United States. Environ. Sci. Technol. 17: 315-324.

Firket, M. (1931) The causes of accidents which occurred in the Meuse Valley during the fogs of December 1930. Bull. Acad. R. Med. Belg. 11[ser. 5]: 683-741.

Franklin, C. A.; Burnett, R. T.; Paolini, R. J. P.; Raizenne, M. E. (1985) Health risks from acid rain: a Canadian perspective. EHP Environ. Health Perspect. 63: 155-168.

Gardner, D. E.; Miller, F. J.; Illing, J. W.; Kirtz, J. M. (1977) Increased infectivity with exposure to ozone and sulfuric acid. Toxicol. Lett. 1: 59-64.

Gearhart, J. M.; Schlesinger, R. B. (1986) Sulfuric acid-induced airway hyperresponsiveness. Fundam. Appl. Toxicol. 7: 681-689.

Gearhart, J. M.; Schlesinger, R. B. (1988) Response of the tracheobronchial mucociliary clearance system to repeated irritant exposure: effect of sulfuric acid mist on structure and function. Exp. Lung Res.: in press.

Godleski, J. J.; Melnicoff, M. J.; Sadri, S.; Garbeil, P. (1984) Effects of inhaled ammonium sulfate on benzo[a]pyrene carcinogenesis. J. Toxicol. Environ. Health 14: 225-238.

Grose, E. C.; Richards, J. H.; Illing, J. W.; Miller, F. J.; Davies, D. W.; Graham, J. A.; Gardner, D. E. (1982) Pulmonary host defense responses to inhalation of sulfuric acid and ozone. J. Toxicol. Environ. Health 10: 351-362.

Holma, B. (1985) Influence of buffer capacity and pH-dependent rheological properties of respiratory mucus on health effects due to acidic pollution. Sci. Total Environ. 41: 101-123.

Holma, B. (1988) Effects of inhaled acids on airway mucus and its consequences for health. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Hyde, D.; Orthoefer, J.; Dungworth, D.; Tyler, W.; Carter, R.; Lum, H. (1978) Morphometric and morphologic evaluation of pulmonary lesions in beagle dogs chronically exposed to high ambient levels of air pollutants. Lab. Invest. 38: 455-469.

Kagawa, J. (1986) Experimental studies on human health effects of aerosol and gaseous pollutants. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment, and control strategies: proceedings of the second U. S.-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 683-697.

Kleinman, M. T.; Bailey, R. M.; Chang, Y.-T. C.; Clark, K. W.; Jones, M. P.; Linn, W. S.; Hackney, J. D. (1981) Exposures of human volunteers to a controlled atmospheric mixture of ozone, sulfur dioxide and sulfuric acid. Am. Ind. Hyg. Assoc. J. 42: 61-69.

Koenig, J. Q.; Pierson, W. E.; Horike, M. (1983) The effects of inhaled sulfuric acid on pulmonary function in adolescent asthmatics. Am. Rev. Respir. Dis. 128: 221-225.

Koenig, J. Q.; Covert, D. S.; Pierson, W. E. (1988) The effects of inhalation of acid compounds on pulmonary function in allergic adolescent subjects. EHP Environ. Health Perspect.: in press.

Kulle, T. J.; Kerr, H. D.; Farrell, B. P.; Sauder, L. R.; Bermel, M. S. (1982) Pulmonary function and bronchial reactivity in human subjects with exposure to ozone and respirable sulfuric acid aerosol. Am. Rev. Respir. Dis. 126: 996-1000.

Larson, T. V.; Covert, D. S.; Frank, R.; Charlson, R. J. (1977) Ammonia in the human airways: neutralization of inspired acid sulfate aerosols. Science (Washington, DC) 197: 161-163.

Last, J. A.; Warren, D. L. (1987) Synergistic interaction between nitrogen dioxide and respirable aerosols of sulfuric acid or sodium chloride on rat lungs. Toxicol. Appl. Pharmacol. 90: 34-42.

Last, J. A.; Gerriets, J. E.; Hyde, D. M. (1983) Synergistic effects on rat lungs of mixtures of oxidant air pollutants (ozone or nitrogen dioxide) and respirable aerosols. Am. Rev. Respir. Dis. 128: 539-544.

Last, J. A.; Hyde, D. M.; Guth, D. J.; Warren, D. L. (1986) Synergistic interaction of ozone and respirable aerosols on rat lungs. I. Importance of aerosol acidity. Toxicology 39: 247-257.

Lave, L. B.; Seskin, E. P. (1972) Air pollution, climate, and home heating: their effects on U.S. mortality rates. Am. J. Public Health 62: 909-916.

Lave, L. B.; Seskin, E. P. (1977) Air pollution and human health. Baltimore, MD: The Johns Hopkins University Press.

Lawther, P. J.; Waller, R. E.; Henderson, M. (1970) Air pollution and exacerbations of bronchitis. Thorax 25: 525-539.

Leikauf, G.; Yeates, D. B.; Wales, K. A.; Spektor, D.; Albert, R. E.; Lippmann, M. (1981) Effects of sulfuric acid aerosol on respiratory mechanics and mucociliary particle clearance in healthy nonsmoking adults. Am. Ind. Hyg. Assoc. J. 42: 273-282.

Leikauf, G. D.; Spektor, D. M.; Albert, R. E.; Lippmann, M. (1984) Dose-dependent effects of submicrometer sulfuric acid aerosol on particle clearance from ciliated human lung airways. Am. Ind. Hyg. Assoc. J. 45: 285-292.

Lewis, T. R.; Campbell, K. I.; Vaughan, T. R., Jr. (1969) Effects on canine pulmonary function via induced NO_2 impairment, particulate interaction, and subsequent SO_x. Arch. Environ. Health 18: 596-601.

Lewis, T. R.; Moorman, W. J.; Ludmann, W. F.; Campbell, K. I. (1973) Toxicity of long-term exposure to oxides of sulfur. Arch. Environ. Health 26: 16-21.

Lioy, P. J.; Samson, P. J.; Tanner, R. L.; Leaderer, B. P.; Minnich, T.; Lyons, W. (1980) The distribution and transport of sulfate "species" in the New York metropolitan area during the 1977 summer aerosol study. Atmos. Environ. 14: 1391-1407.

Lioy, P. J.; Vollmuth, T. A.; Lippmann, M. (1985) Persistence of peak flow decrement in children following ozone exposures exceeding the national ambient air quality standard. J. Air Pollut. Control Assoc. 35: 1068-1071.

Lioy, P. J.; Spektor, D.; Thurston, G.; Citak, K.; Lippmann, M.; Bock, N.; Speizer, F. E.; Hayes, C. (1987) The design considerations for ozone and acid aerosol exposure and health investigations: the Fairview Lake summer camp-photochemical smog case study. Environ. Int. 13: 271-283.

Lipfert, F. W. (1984) Air pollution and mortality=specification searches using SMSA-based data. J. Environ. Econ. Manage. 11: 208-243.

Lippmann, M. (1985) Airborne acidity: estimates of exposure and human health effects. EHP Environ. Health Perspect. 63: 63-70.

Lippmann, M. (1988) Background on health effects of acid aerosols. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Lippmann, M.; Schlesinger, R. B.; Leikauf, G.; Spektor, D.; Albert, R. E. (1982) Effects of sulphuric acid aerosols on respiratory tract airways. In: Walton, W. H., ed. Inhaled particles V: proceedings of an international symposium organized by the British Occupational Hygiene Association; September 1980; Cardiff, United Kingdom; Ann. Occup. Hyg. 26: 677-690.

Lippmann, M.; Lioy, P. J.; Leikauf, G.; Green, K. B.; Baxter, D.; Morandi, M.; Pasternack, B. S.; Fife, D.; Speizer, F. E. (1983) Effects of ozone on the pulmonary function of children. In: Lee, S. D.; Mustafa, M. G.; Mehlman, M. A., eds. International symposium on the biomedical effects of ozone and related photochemical oxidants; March 1982; Pinehurst, NC. Princeton NJ: Princeton Scientific Publishers, Inc.; pp. 423-446. (Advances in modern toxicology: v. 5).

Lippmann, M.; Gearhart, J. M.; Schlesinger, R. B. (1987) Basis for a particle size-selective TLV for sulfuric acid aerosols. Appl. Ind. Hyg. 2: 188-199.

Loscutoff, S. M.; Cannon, W. C.; Buschbom, R. L.; Busch, R. H.; Killand, B. W. (1985) Pulmonary function in elastase-treated guinea pigs and rats exposed to ammonium sulfate or ammonium nitrate aerosols. Environ. Res. 36: 170-180.

Martin, A. E.; Bradley, W. H. (1960) Mortality, fog and atmospheric pollution:; an investigation during the winter of 1958-59. Mon. Bull. Minist. Health Public Health Lab. Serv. G. B. 19: 56-73.

Mazumdar, S.; Schimmel, H.; Higgins, I. T. T. (1982) Relation of daily mortality to air pollution: an analysis of 14 London winters, 1958/59-1971/72. Arch. Environ. Health 37: 213-220.

Morandi, M. T.; Kneip, T. J.; Cobourn, W. G.; Husar, R. B.; Lioy, P. J. (1983) The measurement of H_2SO_4 and other sulfate species at Tuxedo, New York with a thermal analysis flame photometric detector simultaneously collected quartz filter samples. Atmos. Environ. 17: 843-848.

Naumann, B. D.; Schlesinger, R. B. (1986) Assessment of early alveolar particle clearance and macrophage function following an acute inhalation of sulfuric acid mist. Exp. Lung Res. 11: 13-33.

Ostro, B. (1984) A search for a threshold in the relationship of air pollution to mortality: a reanalysis of data on London winters. EHP Environ. Health Perspect. 58: 397-399.

Ozkaynak, H.; Spengler, J. D. (1985) Analysis of health effects resulting from population exposures to acid precipitation precursors. In: Conference on health effects of acid precipitation; November 1984; Research Triangle Park, NC. EHP Environ. Health Perspect. 63: 45-55.

Ozkaynak, H.; Thurston, G. D. (1987) Associations between 1980 U.S. mortality rates and alternative measures of airborne particle concentration. Risk Anal. 7: 449-461.

Pierson, W. R.; Brachaczek, W. W.; Truex, T. J.; Butler, J. W.; Korniski, T. J. (1980) Ambient sulfate measurements on Allegheny Mountain and the question of atmospheric sulfate in the northeastern United States. Ann. N. Y. Acad. Sci. 338: 145-173.

Raizenne, M. E.; Hargreave, F.; Sears, M.; Spengler, J.; Stern, B.; Burnett, R. (1987) Exercise and lung function responses during an air pollution episode in young females with airway hyperresponsiveness to methacholine. Am. Rev. Respir. Dis. 135: A343.

Raizenne, M. E.; Stern, B.; Burnett, R.; Franklin, C. A.; Spengler, J. D. (1988) Acute lung function responses to ambient acid aerosol exposures in children. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Sackner, M. A.; Ford, D.; Fernandez, R.; Cipley, J.; Perez, D.; Kwoka, M.; Reinhart, M.; Michaelson, E. D.; Schreck, R.; Wanner, A. (1978) Effects of sulfuric acid aerosol on cardiopulmonary function of dogs, sheep, and humans. Am. Rev. Respir. Dis. 118: 497-510.

Sackner, M. A.; Dougherty, R. L.; Chapman, G. A.; Cipley, J.; Perez, D.; Kwoka, M.; Reinhart, M.; Brito, M.; Schreck, R. (1981) Effects of brief and intermediate exposures to sulfate submicron aerosols and sulfate injections on cardiopulmonary function of dogs and tracheal mucous velocity of sheep. J. Toxicol. Environ. Health 7: 951-972.

Schlesinger, R. B. (1984) Comparative irritant potency of inhaled sulfate aerosols - effects on bronchial mucociliary clearance. Environ. Res. 34: 268-279.

Schlesinger, R. B. (1987) Functional assessment of rabbit alveolar macrophages following intermittent inhalation exposures to sulfuric acid mist. Fundam. Appl. Toxicol. 8: 328-334.

Schlesinger, R. B. (1988) Factors affecting the response of lung clearance systems to acid aerosols: the role of exposure concentration, exposure time, and relative acidity. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Schlesinger, R. B.; Gearhart, J. M. (1986) Early alveolar clearance in rabbits intermittently exposed to sulfuric acid mist. J. Toxicol. Environ. Health 17: 213-220.

Schlesinger, R. B.; Gearhart, J. M. (1987) Intermittent exposures to mixed atmospheres of nitrogen dioxide and sulfuric acid: effect on particle clearance from the respiratory region of rabbit lung. Toxicology 44: 309-319.

Schlesinger, R. B.; Lippmann, M.; Albert, R. E. (1978) Effects of short-term exposures to sulfuric acid and ammonium sulfate aerosols upon bronchial airway function in the donkey. Am. Ind. Hyg. Assoc. J. 39: 275-286.

Schlesinger, R. B.; Halpern, M.; Albert, R. E.; Lippmann, M. (1979) Effect of chronic inhalation of sulfuric acid mist upon mucociliary clearance from the lungs of donkeys. J. Environ. Pathol. Toxicol. 2: 1351-1367.

Schlesinger, R. B.; Naumann, B. D.; Chen, L. C. (1983) Physiological and histological alterations in the bronchial mucociliary clearance system of rabbits following intermittent oral or nasal inhalation of sulfuric acid mist. J. Toxicol. Environ. Health 12: 441-465.

Schlesinger, R. B.; Chen, L.-C.; Driscoll, K. E. (1984) Exposure-response relationship of bronchial mucociliary clearance in rabbits following acute inhalations of sulfuric acid mist. Toxicol. Lett. 22: 249-254.

Schrenk, H. H.; Heimann, H.; Clayton, G. D.; Gafafer, W. M.; Wexler, H. (1949) Air pollution in Donora, Pa.: epidemiology of the unusual smog episode of October 1948, preliminary report. Washington, DC: Federal Security Agency, Public Health Service; Public Health Bulletin no. 306.

Schwartz, J.; Marcus, A. H. (1986) Statistical reanalyses of data relating mortality to air pollution during London winters 1958-1972. Washington, DC: U. S. Environmental Protection Agency, Office of Policy, Planning and Evaluation.

Speizer, F. E. (1988) Studies of acid aerosols in six cities and in a new multicity investigation: design issues. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Spektor, D. M.; Leikauf, G. D.; Albert, R. E.; Lippmann, M. (1985) Effects of submicrometer sulfuric acid aerosols on mucociliary transport and respiratory mechanics in asymptomatic asthmatics. Environ. Res. 37: 174-191.

Spektor, D. M.; Yen, B. M.; Lippman, M. (1988) Effect of concentration and cumulative exposure of inhaled sulfuric acid on tracheobronchial particle clearance in healthy humans. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Spengler, J. D.; Allen, G. A.; Foster, S.; Severance, P.; Ferris, B., Jr. (1986) Sulfuric acid and sulfate aerosol events in two U.S. cities. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P., eds. Aerosols: research, risk assessment and control strategies: proceedings of the 2nd U. S.-Dutch internationalsymposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 107-120.

Spengler, J. D.; Keeler, G. J.; Koutrakis, P.; Raizenne, M. (1988) Exposure to acidic aerosols. In: International symposium on the health effedts of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Stacy, R. W.; Seal, E., Jr.; House, D. E.; Green, J.; Roger, L. J.; Raggio, L. (1983) A survey of effects of gaseous and aerosol pollutants on pulmonary function of normal males. Arch. Environ. Health 38: 104-115.

Stara, J. F.; Dungworth, D. L.; Orthoefer, J. G.; Tyler, W. S., eds. (1980) Long-term effects of air pollutants: in canine species. Cincinnati, OH: U. S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-80-014. Available from: NTIS, Springfield, VA; PB81-144875.

Stevens, R. K.; Dzubay, T. G.; Russwurm, G.; Rickel, D. (1978) Sampling and analysis of atmospheric sulfates and related species. Atmos. Environ. 12: 55-68.

Stevens, R. K.; Dzubay, T. G.; Shaw, R. W., Jr.; McClenny, W. A.; Lewis, C. W.; Wilson, W. E. (1980) Characterization of the aerosol in the Great Smoky Mountains. Environ. Sci. Technol. 14: 1491-1498.

Tanner, R. L.; Leaderer, B. P.; Spengler, J. D. (1981) Acidity of atmospheric aerosols: a summary of data concerning their chemical nature and amounts of acid. Environ. Sci. Technol. 15: 1150-1153.

Thurston, G. D.; Waldman, J. (1987) Acid aerosol transport episodes in Toronto, Ontario. Presented at: 80th annual meeting of the Air Pollution Control Association; New York, NY. Pittsburgh, PA: Air Pollution Control Association; paper no. 87-89.9.

Thurston, G. D.; Ito, K.; Lippmann, M.; Hayes, C. (1988) Re-examination of London, England mortality in relation to exposure to acidic aerosols during 1963-1972 winters. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

U. S. Environmental Protection Agency. (1982a) Air quality criteria for particulate matter and sulfur oxides. Research Triangle Park, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report nos. EPA-600/8-82-029aF-cF. 3v. Available from: NTIS, Springfield, VA; PB84-156777.

U. S. Environmental Protection Agency. (1982b) Review of the national ambient air quality standards for particulate matter: assessment of scientific and technical information, OAQPS staff paper. Research Triangle Park, NC: Office of Air Quality Planning and Standards; EPA report no. EPA-450/5-82-001. Available from: NTIS, Springfield, VA; PB82-177874

U. S. Environmental Protection Agency. (1986) Second addendum to air quality criteria for particulate matter and sulfur oxides (1982): assessment of newly available health effects information. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA/600/8-86/020F.

United Kingdom Ministry of Health. (1954) Mortality and morbidity during the London fog of December 1952. London, United Kingdom: Her Majesty's Stationary Office. (Reports on public health and medical subjects no. 95).

Utell, M. J.; Morrow, P. E.; Hyde, R. W. (1982) Comparison of normal and asthmatic subjects' responses to sulphate pollutant aerosols. In: Walton, W. H., ed. Inhaled particles V: proceedings of an international symposium organized by the British Occupational Hygiene Association; September 1980; Cardiff, United Kingdom; Ann. Occup. Hyg. 26: 691-697.

Utell, M. J.; Morrow, P. E.; Speers, D. M.; Darling, J.; Hyde, R. W. (1983) Airway responses to sulfate and sulfuric acid aerosols in asthmatics: an exposure-response relationship. Am. Rev. Respir. Dis. 128: 444-450.

Utell, M. J.; Morrow, P. E.; Hyde, R. W. (1984) Airway reactivity to sulfate and sulfuric acid aerosols in normal and asthmatic subjects. J. Air Pollut. Control Assoc. 34: 931-935.

Utell, M. J.; Morrow, P. E.; Hyde, R. W. (1985) Latent development of airway hyperreactivity in human subjects after sulfuric acid aerosol exposure. J. Aerosol Sci. 14: 202-205.

Utell, M. J.; Morrow, P. E.; Bauer, M. A.; Hyde, R. W.; Schrek, R. M. (1986) Modifiers of responses to sulfuric acid aerosols in asthmatics. In: Aerosols: formation and reactivity. London: Pergamon Press.

Ware, J. H.; Ferris, B. G., Jr.; Dockery, D. W.; Spengler, J. D.; Stram, D. O.; Speizer, F. E. (1986) Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. Am. Rev. Respir. Dis. 133: 834-842.

Warren, D. L.; Last, J. A. (1987) Synergistic interaction of ozone and respirable aerosols on rat lungs: III. ozone and sulfuric acid aerosol. Toxicol. Appl. Pharmacol. 88: 203-216.

Wichmann, H. E.; Mueller, W.; Allhoff, P.; Beckmann, M.; Bocter, N.; Csicsaky, M. J.; Jung, M.; Molik, B.; Schoenberg, G. (1988) Health effects during a smog-episode in West Germany in 1985. In: International symposium on the health effects of acid aerosols: addressing obstacles in an emerging data base; October 1987; Research Triangle Park, NC. EHP Environ. Health Perspect.: in press.

Wolff, R. K.; Silbaugh, S. A.; Brownstein, D. G.; Carpenter,R. L.; Mauderly, J. L. (1979) Toxicity of 0.4- and 0.8-μm sulfuric acid aerosols in the guinea pig. J. Toxicol. Environ. Health 5: 1037-1047.

8. RESEARCH NEEDS

Throughout earlier chapters in this issue paper, numerous gaps in the current data base for acid aerosols were noted. The present chapter summarizes some of the more crucial research needs that are critical to be addressed in order to provide a firmer basis by which to judge the need for listing ambient aerosols as a criteria air pollutant and for developing any consequent criteria and standards. The research needs discussed reflect inputs from chapter authors of this report, external peer reviewers of drafts of this document, and EPA scientists and represent critical areas where significant gaps exist in the data base concerning acid aerosols and associated health effects. They are identified below by subject area and include needs related to: characterization and exposure; animal toxicology studies; controlled human exposure studies, and epidemiological research.

8.1 CHARACTERIZATION AND EXPOSURE

Development and Evaluation of Measurement Methods -- Currently, there are a multitude of techniques to detect various acid species in the atmosphere. Ideally, before initiating extensive studies to characterize components, levels, and distribution of ambient acid aerosols, it would be desirable to have a consensus by the scientific community on measurement techniques that are accepted as reliable and that reflect the indicator(s) of concern from health effects studies. Available health studies have not unequivocally identified a unique entity as the "correct" indicator, although the available evidence suggests that either the H^+ of strong acids or sulfuric acid (H_2SO_4) specifically is the toxicologically important component. Therefore, until and unless health studies can define the species of concern more explicitly, it is desirable to measure individual acid species (both in particles and gases) and more inclusive measurements of titratable H^+, which can include strong acidity and weak acidity, if desired.

There are a number of similar techniques, used by different research groups, which are based on removal of acidic and basic gases by various types of denuders, collection of acid particles on filters, preservation of the samples from NH_3, and analysis for H^+ by pH measurements or titration, and analysis of SO_4^{2-}, NO_3^-, NO_2^-, Cl^-, and NH4+ by ion chromatography. These can give time resolution of as low as one or a few hours or for periods of 24 hours or longer.

H_2SO_4 may be determined semicontinuously by flame photometry using a temperature-cycled diffusion denuder tube. However, 95% of the aerosol acid sulfate is typically not in the form of H_2SO_4. Other techniques utilizing thermal treatment applications have been used for semicontinuous measurements and measure most of H_2SO_4 and possibly NH_4HSO_4. In any event, a program is needed to evaluate existing methods and to develop or modify techniques, with a goal of developing recommended approaches that are accepted by the scientific community and which will thereby provide some uniformity by which to evaluate ambient conditions and, ultimately, human exposures to acid aerosols.

Application of Measurement Techniques -- There are a variety of applications that place different requirements on measurement techniques. In conjunction with methods development and evaluation, the range of potential applications needs to be considered. Research applications require a variety of special measurements but do not necessarily require low cost, unattended use, or easy operation. Characterization studies, which need to be conducted over longer time periods for ambient, indoor, and personal exposure, place additional constraints on measurement techniques in terms of time resolution, reliability and accuracy, and ease of operation. For these purposes, scientific acceptance and good quality control are essential. Measurements must be as complete as possible in terms of species measured.

Both batch and continuous (or at least semicontinuous) techniques will be needed for research and characterization studies. Continuous techniques are typically more expensive to setup and more difficult to operate than batch techniques, but provide information not available from batch measurements and may be cheaper on a per-sample basis.

An overriding concern for various applications and sampling strategies is their relevance to available health effects information. For example, there appears to be a significant diurnal variation in acid levels; the time resolution of batch measurements ideally would differentiate this variation (e.g., 6-hour intervals) yet would still be compatible with longer term integrated measurement, and thus allow extrapolation to a variety of possible exposure scenarios.

Characterization of Ambient Acid Levels -- At present, there are extremely limited data to characterize ambient acid aerosol levels. Once appropriate measurement techniques are available, an ambient characterization study should be conducted to give a better indication of the potential exposure to atmosphere acids. Sampling sites should include, as a minimum, an urban and an upwind (in terms of expected acidity) station. Species measured should include H_2SO_4 and strong acidity, and for gases, HNO_3, HNO_2, and NH_3. Measurement of other species and parameters would be useful, especially fine particle mass, SO_4^{2-}, NO_3^-, O_3, SO_2, and NO_2. Time resolution should be adequate to characterize the diurnal cycle. Geographic coverage should include, as a minimum, a site in the mid-west source region, a site in the sulfate impacted NY or PA area, and two sites farther south in the east. At least two should be in areas with acid soil and therefore presumably low NH_3.

Additional Characterization Needs -- Several factors that may affect concentration-response relationships for ambient acid aerosols need further study. These include ambient size distributions of acid particles, ammonia neutralization, aerosol dynamics and chemistry, and spatial and temporal relationships.

Penetration and deposition in the respiratory tract is a function of particle size. Acidity is expected to be confined to the fine particles (0 - 2.5 µm) but the possibility of acidity in coarse particles capable of penetrating the tracheobronchial region of the respiratory tract should be examined. Within the fine fraction, the exact particle size, and the distribution between the nuclei mode (0 - 0.1 µm) and the fine mode (0.1 - 2.5 µm) needs to be determined for various concentrations and pollutant conditions.

Changes in particle size with increasing relative humidity, as encountered in the respiratory system, can be modeled for pure compounds. For acid particles which contain nitrate and soluble organics as well as sulfate, additional theoretical and experimental work is needed.

With respect to acid fog, current research is limited to characterization of bulk fog or cloud water. Unfortunately the efficiency of the collectors are low and not well known for sizes where lung deposition is high. Measurement techniques are adequate but need to be applied to size-differentiated samples.

Measurements have shown that NH_3 reacts rapidly with pure H_2SO_4 aerosol. However, in the atmosphere acid particles may be coated with a film which will impede the diffusion of NH_3 into the liquid droplet. Thus, it may be that acid particles can coexist with NH_3. Information on the rate of neutralization is needed for design of new measurement techniques, to model acid air quality, to calculate exposure, and to understand the role of endogenous NH_3 in influencing the acidity of acid particles in the respiratory system.

Current research suggests the occurrence, especially during summer episodes, of a strong diurnal pattern with sulfate and acidity both peaking between 12 noon and 6 pm. Since health effects may depend on the short-term, high-level exposures, over a threshold, measurement techniques must be adequate to resolve these peaks. Thus, batch measurements with one-hour resolution or continuous or semicontinuous measurements may be required.

Acidity may come from regional scale sulfate pollution which is almost continuous in some parts of the country and more episodic in others. acidity may also come from near-source impacts of plumes. Exposure studies will need to cover these spatial determinants of ambient acidity.

Exposure -- If health effects studies support health concerns with acid aerosol at expected ambient exposure levels, personal monitors and personal exposure studies will be needed to augment available ambient data. This should include indoor measurements to study penetration of outdoor acidity into indoor environments in homes, schools, and offices; the influence of indoor NH_3 sources; and the possible generation of acid aerosol by indoor combustion sources. Activity models should be available from other studies.

Air Quality Models -- At some point, it may become necessary to model acid aerosol air quality. Over the next few years, major advances in air quality models are expected in terms of transport and removal processes and sulfuric acid formation (from the Regional Acid Deposition Model), and aerosol size distribution from Visibility and Fine Particle Models. There are several considerations which will be especially important for an acid aerosol model which may not be adequately addressed in existing programs. It may be appropriate to add or put more emphasis on these considerations. They include NH_3 emissions and influence of soil acidity on NH_3 emissions and removal, and diurnal variations in acidity and sulfate concentration. More effort may be needed to differentiate between pollutant processes in the near ground-level well-mixed layer, and in that portion of the well-mixed layer which is isolated from the ground during night-time and early morning.

8.2 ANIMAL TOXICOLOGICAL STUDIES

Identification of the Hazardous Chemical Species -- Concern about the health risks of acidic aerosols is derived from epidemiological studies, most of which did not include direct acid measurements in their exposure assessment, and controlled human and animal studies of H_2SO_4 and other less acidic sulfate species. While this work forms the basis for numerous research needs, there is a major need to identify the causative chemical species so that future health and monitoring studies are properly directed and that ultimately the causative species can be controlled. The relative potency of various acid species needs further study; most work has focused on H_2SO_4 but NH_4HSO_4 may dominate ambient aerosol acidity of times. In addition, there is a need to understand the relative role of the cation and the anion associated with various acid species, and the toxicological effects of acidic particles compared to acidic gases. A more complex issue has arisen from recent research by Dr. Amdur and her colleagues (see Chapter 4). They found that H_2SO_4 adsorbed onto ultrafine zinc oxide particles was 3 to 10 times as potent in changing pulmonary function as an equivalent-sized aerosol of H_2SO_4 mist. This raises several questions, not only for H_2SO_4, but also for HCl since it is emitted from hazardous and municipal waste incinerators, perhaps in association with particles.

Determination of Concentration Times Time (C x T) Relationships -- Health effect outcomes are dependent on many factors, with C x T being one of the major ones. Ambient air patterns of acids, as of other pollutants, are not steady-state, so it is critical to determine which exposure patterns are of greater risk and hence must be monitored in research studies, and be controlled if control is warranted. Given the paucity of C x T health and monitoring data, it is important to develop a research strategy between both health and monitoring scientists so that each may be guided by the other iteratively. The alternative is a plethora of health data bearing no relationship to ambient exposures or a plethora of monitoring data with averaging times uninterpretable with respect to health risk. Health study components would focus on only a few sensitive indicators of response, perhaps clearance and/or pulmonary function. Focus is necessary to simplify what will be a complex matrix design.

Determine Influence of Pattern of Exposure on Effects -- This topic has elements in common with the C x T studies described above, but focuses more on the effects of timing of the pattern of exposure vis-a-vis pattern of response. Only rarely are delayed responses studied, although they can occur and may provide important guidance to design and interpretation of human clinical and epidemiological studies. In the Cincinnati dog study (see Chapter 4) in which dogs exposed to H_2SO_4 plus SO_2 were examined 2 years post-exposure, pulmonary function effects were progressive, arguing further for the incorporation of delayed response studies in experimental designs. Another issue of importance to explore is the response to short-term repeated exposures. Over a week, the pattern of pulmonary function responses changes, in some cases worsening and in others plateauing. To interpret the degree of adversity, it is necessary to know whether there are "silent" changes to one endpoint that progress while other endpoints adapt, as is the case with ozone.

Quantitative Animal to Man Extrapolation of Effective Acid Exposures and Regional Pulmonary Deposition in Man -- It is reasonably expected that animal studies will provide cause-effect data on the chronic effects of acids, mechanisms of effects, and the full range of effects, thereby providing information unavailable from epidemiological or human clinical studies. These animal data are therefore of great importance to risk assessment, but quantitative extrapolation to man is required. This extrapolation must be rigorous inasmuch as small differences in effective concentrations have major impacts on risk management. To achieve the animal-to-man extrapolation, two primary factors must be considered: dosimetry and species sensitivity. Research on the relationship between concentration and delivered dose in animals and man will be complex since 1) acids are hygroscopic aerosols for which more fundamental data are needed, 2) neutralization by breath ammonia and, in whole body exposure, ammonia from excrement, can be important, 3) tissue dose will be highly dependent on mucus buffering capacity, requiring data on mucus biochemistry, and 4) microdosimetry (i.e., dose within lung regions) is quite important since health studies on a single endpoint (i.e., clearance) show responses to be dependent on regional dose. Of course, other dosimetric factors are equally important, but acids present some special cases. It is also of interest to compare dosimetric relationship within subpopulations of "man", e.g., normal, asthmatic, exercising, etc. Understanding these relationships will enhance the accuracy of predicting susceptibility factors, since ultimately it is dose that causes an effect. Even once dose-equivalency in different species is known, species sensitivity to a given dose is likely to have some differences which must be quantified and linked with dosimetry to provide a full extrapolation. It is already recognized that the guinea pig is more sensitive for some endpoints than other animal species to a given inhaled concentration. How does the sensitivity of a guinea pig compare to "man", whether "he" be normal, asthmatic, or otherwise more susceptible?

Determine the Effects of Acids(s) on Development of Chronic Lung Disease -- There are sufficient data to hypothesize that long-term exposure to low levels of H_2SO_4 may cause chronic bronchitis. Because of the significance of these findings, it is essential to test the hypothesis. Several approaches are of interest. A few would include conducting a study similar to the rabbit study of Schlesinger et al. (see Chapter 4) in at least one additional species; repeating the Schlesinger et al., study at a lower concentration; increasing the knowledge of the relationship between alterations in lung clearance and the development of chronic bronchitis; applying state-of-the-art lung morphometric methods in a time-course study.

Define a Fuller Range of Classes of Effects of Acids -- Generally, the literature on the health effects of acids is sparse, with the more important findings resulting from the application of newer methods and technologies. Recently, low levels of H_2SO_4 have been observed to result in inflammatory responses and effects on alveolar macrophages. These changes have implications to the development of chronic lung disease. The alveolar macrophage effects and lung clearance effects may portend decrements in host resistance to infection, most probably viral infection since bacterial infectivity is apparently not affected. Taking the literature as a base, several findings require follow-up so that risk potential can be understood. As examples, is the influx of neutrophils associated with other inflammatory changes; are defenses against viral infection compromised?

Determination of Susceptible Subpopulations -- Several subpopulations are known or suspected to be more susceptible to acid aerosols. While some of this research is incorporated under extrapolation modeling discussed earlier, animal toxicological research on this topic is needed to supplement human studies to explore mechanisms more fully.

Interaction of H_2SO_4 With Other Co-occurring Common Pollutants -- The issue of the enhanced potency of H_2SO_4 adsorbed onto particles was discussed briefly under the first recommendation in this section and will not be repeated here. Sulfuric acid in association with other pollutants such as ammonium sulfate, O_3, and NO_2 has been found to be additive, synergistic, antagonistic or non-influential, depending upon the endpoint, the co-pollutant, and whether the exposure was in sequence or in mixture. From a risk perspective, understanding the synergism is of major importance. Such studies need to be designed to mimic ambient occurrences of H_2SO_4 and co-pollutant exposures, insofar as possible. For example, the temporal relationship and concentration ratios of O_3 and H_2SO_4 that actually occur should be investigated for effects using sensitive endpoints such as edema, lung clearance, and other endpoints as well, since there can be a dependence on endpoint. Once the phenomenon is understood better, mechanism studies are needed to enable predictions of interactions in risk assessments. Such predictions are important since it is not feasible to collect data on every potential interaction of interest.

8.3 CONTROLLED HUMAN EXPOSURE STUDIES

Studies of Adolescent Asthmatics -- Further studies of adolescent asthmatics are required to confirm the apparent susceptibility of this patient group. Specific attention should be focused on exposures to acid aerosols in the concentration range of 0-200 $\mu g/m^3$. As an adjunct to such studies, determination of differences in mucus buffering capacity or oral and airway ammonia levels in young asthmatics should be made.

Studies of Mucociliary Clearance in Humans -- Further work on mucociliary clearance measurements in humans is needed, emphasizing standardization of measurement methods and independent confirmation of findings. This work should focus on estimation of airway acid burdens and, ultimately, identification of acid deposition "hot spots". Effects of longer (2-8 h) exposures to lower concentrations (0-100 $\mu g/m^3$) of acid aerosol are necessary to examine further the predictive validity of the concentration-time product model. Further basic work is needed to attempt to understand the large "normal" range of mucociliary clearance rates.

Studies of Airway Hyperreactivity -- Further work on the relationship between induction of airway hyperreactivity and acid aerosol exposure is needed. It is important to determine whether acids induce airway inflammatory responses that may be associated with hyperreactivity. At present, only hyperresponsiveness to carbachol has been demonstrated. Investigation of post-exposure reactivity to other stimuli, such as histamine, methacholine, or antigens, would help to clarify the specific or general nature of the airway response.

Titratable Acids -- All studies should report the titratable acidity of the aerosol in addition to particle size distribution, acid concentration of liquid that is aerosolized, and mass concentration of aerosol.

Studies of Hyperresponsive Subjects -- Efforts should be made to focus on the susceptible members of the population. Specifically, responses of hyperreactive subjects should be confirmed. Further study of hyperresponsive individuals should be initiated to attempt to discern possible mechanisms of reactivity. Both longer-duration and repeated-exposure studies in humans with acid aerosols will be necessary to evaluate cumulative effects and possible adaptive responses. The possibility that repeated acid aerosol exposure may result in airway hyperresponsiveness should be evaluated.

Buffering Capacity of Airway Secretions -- More information is needed regarding the ability of airway secretions to buffer inhaled acids. Susceptible subjects need to be identified. Regional variation within the lung of buffer capacity needs to be better defined. Buffering capacity of mucus from asthmatics needs to be further evaluated.

Variation of Ammonia Production -- Interindividual, regional, and species variation in ammonia production must also be evaluated. When possible, studies should measure ammonia levels in conjunction with acid aerosol exposures.

Effects on Respiratory Epithelium -- The effects of acid aerosols on the respiratory epithelium need to be studied more extensively. Changes in epithelial permeability are expected to occur as a result of acute acid inhalation.

Small Airway Effects -- Improved methodology for non-invasive evaluation of small-airway responses is necessary because aerosol deposition models indicate that a large portion of inhaled acid in the ambient size range is deposited in the vicinity of the alveoli and respiratory bronchioles.

Effects of Mixtures of Pollutants -- Effects of acid in mixtures of other pollutants need to be studied in more detail. Specifically, exposure sequences and simulation of ambient exposures should be examined. Both ozone and H_2SO_4 appear to cause increased epithelial permeability. Further examination of the effects of ozone and H_2SO_4 mixtures thus appears warranted. Further work with asthmatics exposed to mixtures of SO_2 and acid or possibly NO_2 and acid is also needed.

Delayed Responses -- Further study of delayed response, seen in studies of normals and asthmatics, is needed to evaluate possible mechanisms of delayed effects of potential importance. Specifically, a series of follow-up measurements is necessary to evaluate delayed effects and their time course.

Other Acids -- There have been a substantial number of studies on sulfuric acid aerosols. Further work should be conducted using vapor phase acids such as HNO_3 and HCl, as well as NH_4HSO_4, which may be a major contributor to aerosol acidity.

Deposition and Neutralization of Hygroscopic Acid Particles -- Several models have been developed to describe deposition and neutralization of hygroscopic acidic particles. Further experimental work is necessary to verify these models and to provide information that might explain the differences between model prediction.

8.4 EPIDEMIOLOGY STUDIES

Epidemiology provides an approach for directly studying the effects of ambient acid aerosol mixtures on human health endpoints. Such studies conducted to date, however, have been markedly limited due to the lack or sparsity of actual acid measurements or to the relatively low concentrations of acids present at the time of particular studies. Nevertheless, the data derived from epidemiological and other types of studies thus far do suggest that certain health endpoints are more likely than others to be affected by acid aerosols.

Based on the available epidemiological, controlled human exposure, and animal toxicological studies, future research should clearly include evaluation of pulmonary function and respiratory diseases as possible health endpoints. Increased incidence or aggravation of respiratory diseases or symptoms, such as persistently increased cough and phlegm, bronchitis, and asthma have all been indirectly implicated. Specifically, chronic bronchitis rates have been consistently elevated in those situations where it was also likely or confirmed that ambient air acid levels were elevated. It is also possible that well-conducted epidemiological studies of short-term exposure effects on lung function may yield significant effects, especially if geographic study locations can be found with higher ambient acid aerosol levels than those typically seen thus far in the summer camp studies discussed in Chapter 6. As for asthmatics, a reactive population not taking medication may be indicated as a group to study. Hyperresponsiveness and delayed responses may need to be evaluated. Also, since inflammatory processes are found to increase in the airways following exposure to acid, studies examining reversible changes in pulmonary function may be appropriate.

Further development of better methods to more accurately measure ambient acid levels (see Section 8.1) and the deployment of adequate monitoring sites are crucial for the success of future epidemiological study efforts. Realistically, given anticipated funding limitations, increasing support to already ongoing large-scale epidemiology investigations, so that they can be expanded to include sufficient acid aerosol aerometric measurements and analysis of health endpoints in relationship to such measurements will probably provide the best near-term opportunity to notably improve the acid aerosols health data base. For example, existing ongoing or planned epidemiology studies should be extended to include additional health endpoints, larger numbers of subjects, increased numbers of chemical species measured, additional study areas, and greater numbers of monitoring sites in study areas. Some specific examples of what might be done are concisely highlighted below.

New Harvard Multicity Investigation -- (Primary Sponsors NIEHS and Health and Welfare, Canada). This study is to directly assess the chronic effects of acid aerosol on the respiratory health of children. This prevalence cross-sectional study is discussed in Section 6.4. It is designed to clarify the possible role acid aerosols may play in chronic respiratory disease that was suggested in earlier epidemiology studies. Additional funding could be used to improve acid aerosol exposure assessment and expedite reporting of results.

Canadian Hospital Admissions Study -- As discussed in Section 6.2.4 there is a suggestion that acid aerosol levels may be related to respiratory admissions to hospital in Southern Ontario, Canada. Acid aerosol measurements have been obtained in this area during the past two years. Hospital admissions data will become available to the researchers in the near future. Additional funding to expedite analyses and reporting of results would be beneficial.

Studies in the Netherlands -- Several studies underway and planned in the Netherlands would benefit from additional funding and potentially produce data related to the health effects of acid aerosols in a shorter time frame. One ongoing study is designed to examine the long-term effects of pollutants on normal and sensitive adults. Every three years, this prospective study examines respiratory function and symptoms of respiratory disease. The overall goal is to examine the decline of pulmonary function and the onset of chronic respiratory disease. Additional assistance related to the acid aerosol component of the study would be beneficial, e.g., to expand acid aerosol monitoring.

The above study results may be influenced by short-term effects from acute pollutant exposures that affect the general long-term trends. These short-term effects will be examined to clarify this problem. Acid aerosol data would be an important addition to this analysis.

Another acute study in the planning stage is examination of the respiratory effects on children of exposure to pollutant events. Acid aerosol data would be important in this study as well. Of special importance would be to develop monitoring and measurement capabilities sufficient to characterize peak exposures.

Studies in Other Countries -- European study settings provide an opportunity to assess winter excursions of pollutants, including acid aerosols which are not accompanied by elevated ozone as is typical of the summertime episodes in the U.S. Respiratory morbidity in patients of general practitioners in England (see Section 6.2.2) is a potential area of study. Examining acute bronchitis rates in children in relation to acid aerosol exposure is suggested. Preliminary data from a study in West Germany (see Section 6.2.2) suggest that study of respiratory disease and exposure to acid aerosols may be indicated in that Country. Another possible location for a study of respiratory disease in relation to acid aerosol exposure is in Italy in the area of the largest power plant in Europe. Additional study opportunities should be explored in other European countries and elsewhere, e.g., China.

Indoor Exposures -- Preliminary results from chamber studies at Yale University indicate that high indoor exposures to acid aerosols may result from the use of kerosene heaters. Additional research is needed to determine the extent to which these exposures occur in residential settings and if indicated to assess their health effects. This might be effectively accomplished by augmenting the above ongoing epidemiology studies

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